Top-down and Bottom-up: Cognitive Mechanisms in Drug Dependence and Treatment Outcomes

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Statement of Sources

I declare that this report is my own original work and that contributions of others have been duly acknowledged.

_____ Date: _____

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Abstract

Particular cognitive deficits such as attentional biases toward drug related stimuli (driven by low-level 'bottom-up' processes) and problems with inhibiting actions (executive or 'top-down' processes), appear to be associated with substance use disorder. Study used two experiments (One: 7 participants with mean age of 41.7 years, two: 67 participants with mean age 34.3 years) to test the theoretical framework proposed by Manning et. al. (2017). Poorer 'top-down' inhibitory cognition and greater 'bottom-up' drives: (according to the model) should be related to severity of substance use disorder (predicted by the model) correlate with poorer treatment outcomes (early drop out; tested at week 4 and 12). The study findings showed mixed evidence to support the theory underpinning the framework with significant bottom-up compulsivity measure but not top-down response inhibition. The predictions made by the framework were not supported. Previous studies analyzing the relation between cognition and treatment outcomes failed to control for psychological distress and readiness to change. After controlling for other key correlates of treatment dropout (anxiety, and readiness to change), top-down (SST) measure was significantly associated with treatment outcomes. The findings highlight the multifaceted way in which people can remain stuck in substance use disorder.

Substance use disorder (SUD) is one of society's most prevalent health and social problems (AIHW, 2017). Globally, 0.6% per cent of the adult population suffer from SUD (UNODC, 2017). In 2015, SUD was the fifth leading disorder category with an estimated 17 million years of "healthy" life (disability-adjusted life years) lost as a result of premature death and disability (UNODC, 2017). SUD has a significant impact on all aspects of an individual's wellbeing (NIDA, 2009) as well as a larger social and economic burden (UNODC, 2017). Collins and Lapsley (2008) found the total costs of drug use within Australia during 2004/2005 exceeded A$55 billion, with alcohol costing A$15.3 billion, and illicit drugs A$8.2 billion.

A substantial amount of recent psychological research has been conducted in attempts to better understand outpatient treatment outcomes for those presenting with substance use disorder. In 2016–17, around 193,031 clients engaged in government-funded alcohol and drug treatment in Australia (AIHW, 2017). Figure 1 shows the trend patterns for treatment provided by drug type over the last 10 years. Overall the number of treatment episodes provided has increased by 24% over the 10-year period (AIHW, 2017).

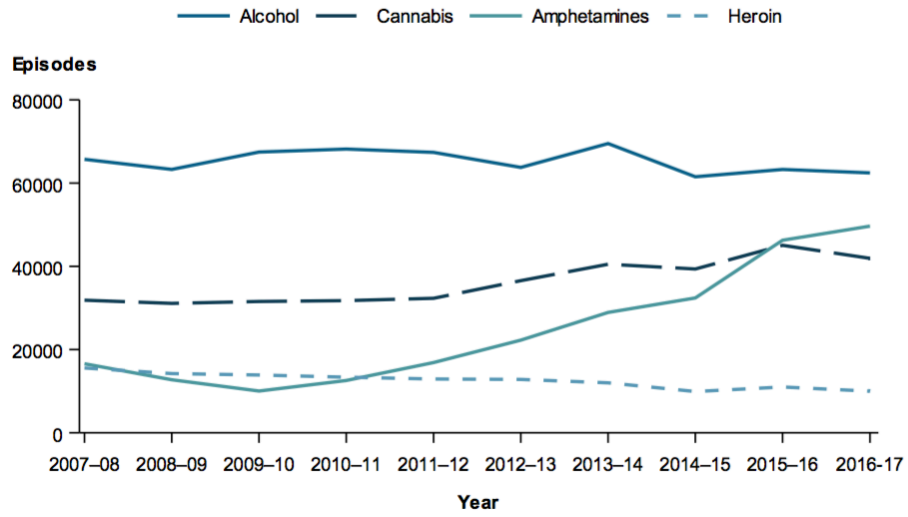


Figure 1. Closed treatment episodes for own drug use, by the four main principal drugs of concern, 2007–08 to 2016–17 (AIHW,2017).

Definition and Symptomatic criteria for SUD in the DSM-5

SUD is characterized in the DSM-5 as significant distress (social, psychological and physical) as a result of as a result of continued drug-taking behaviour (American Psychiatric Association, 2013). Individual substances are addressed as use-specific disorders (i.e. alcohol-use disorder, cannabis-use disorder act.), however, they are all diagnosed according to the same diagnostic criteria (Hasin et. al., 2013). This is because the mechanisms underlying the chronic and chronic effects of drugs are the same. Chronic substance use alters the physical structure of the brain by hijacking the ventral tegmental area and mesolimbic pathway, altering its function after the repeated dopaminergic surge by increasing the dopaminergic neurons when substances are repeatedly drug is administered (Lubman, Yucel & Pantelis, 2004). This, redirecting the individual to seek the addictive substance instead of healthy pleasure seeking (food, sex etc., Dennis & Scott, 2007). Despite negative consequences, people with SUD continue to use these substances (Lubman et al., 2004). These drug-seeking and drug-taking behavioral patterns are consistent across drug type and are exacerbated in chronic users (Elman & Borsook, 2016).

There are 11 symptomatic criteria for SUD in the DSM-5 (American Psychiatric Association, 2013; see table 1). Severity of SUD is measured by criteria count; mild (two to three criteria), moderate (four to five), and severe (six or more; American Psychiatric Association, 2013).

Table 1

Symptomatic criteria for SUD in the DSM-5 (American Psychiatric Association, 2013).

Criteria Grouping	Criteria	N
Impaired Control	Drug use in larger amounts or over a longer period of time than intended	1
	Persistent desire to cut down and problems doing so	2
	Time spent obtaining or recovering from drug effects increases	3
	Craving or strong desire to use	4
Social Impairment	Recurrent drug use resulting in failure to fulfill major role obligations at work, school, or home	5
	Recurrent drug use resulting in recurrent social or interpersonal problems	6
	Given up or reduced important social occupational or recreational activities because of use	7
Risky Use	Recurrent drug use in physically hazardous situations	8
	Continued use despite knowledge of physical OR mental problem exacerbated by drug	9
Physiological adaptation	Tolerance	10
	Withdrawal	11

Psychosocial Treatment

Engagement in treatment programs is necessary for successful treatment outcomes. As SUD is multifaceted disorder and impacts many aspects of a person's wellbeing, psychosocial treatment is tailored to the individual rather than the substance used (NIDA, 2009). Psychosocial, 'talk-based therapy' is a common treatment and front-line intervention for problems with cannabis, alcohol and amphetamine use (AIHW, 2017). Common interventions include cognitive behavior therapy (CBT), goal setting, relapse prevention tenancies, motivational enhancement therapy (MET), psychodynamic therapy/interpersonal therapy, case management, and group, marital, and family therapies (Kilmas et. al., 2014).

The current state of the literature suggests that psychosocial interventions are the most effective treatments for cannabis (Gates, et. al., 2017) and methamphetamine (Perez-Mana, et.al., 2013) use disorder, and are effective interventions for alcohol use disorder when paired with with pharmacological treatment options (Kilmas et. al., 2014).

Prominence of Treatment Drop-out and Relapse

In 2016–17 overall, clients seeking treatment for their own drug use received an average of 1.6 treatment episodes (AIHW,2017). The overall average in Tasmania being 1.4 treatment episodes (AIHW, 2017). To see symptom improvement through treatment engagement, a minimum of three months is recommended with symptom improvement increasing linearly with length of treatment engagement (Katz, et. al. 2004). Studies show consistent treatment engagement contribute to greater rates of abstinence (Winters, Fawkes, Fahnhorst, Botzet, & August, 2007). Cannabis using populations showed greater treatment outcome to be associated with consistent psychosocial treatment (Gates, et. al., 2017).

However, dropout rates for those engaged in outpatient 'talk-based' therapy were alarmingly high with more than half (55%) engaged in therapy for less than a month (AIHW, 2017). Dropout after three months increased by 24%, while after twelve months were over 75% (AIHW, 2017). Dropout rates have shown to be consistent across drug type (Sofuglu, DeVito, Waters, & Carroll, 2013), with similar trends internationally. In the United States, drop-out rates within the first month are approximately 30% and approximately 50% within the first 3 months (Palmer, Murphy, Piselli, & Ball, 2013; Loveland & Driscoll, 2014). Similar rates (23-50%

drop-outs in 8 weeks) have been observed in Europe (Simsek, Dinc, Ogel, 2018), South America (57% in first month; Passor & Camacho, 2000) and India (61.3% in first month; Basu et. al, 2017).

Treatment approaches historically have adopted a disease based framework with abstinence being the main goal (Worley et.al., 2012). However, it is not uncommon for relapse to occur many times in the process of recovery (Worley et.al., 2012). Clinicians therefore lean towards a harm reduction approach with use reduction being the immediate goal and abstinence the long term goal (Worley et.al., 2012). Relapse, following a period of abstinence, is a logical consequence of a behavioural conditioning process, as drug seeking-habits are reactivated by drug-cues (Robbins & Everitt, 1999). Triggering events can be classed into three main categories, the administration of a similar drug, the presence of a drug-conditioned stimulus and/or the induction of a state of stress (Robbins & Everitt, 1999).

Prevalence of Cognitive Impairment in SUD populations

Studies have consistently found impairments in cognitive functioning, such as executive memory, decision making, attention and response inhibition to be factors contributing to therapy engagement (Manning, Verdejo-Garcia & Lubman, 2017). Illicit substances all produce some impairment in neuropsychological mechanisms, as well as additional substance-specific impairments (Fernandez-Serrano, Perez-Garcia, & Verdejo-Garcia, 2011). Prolonged substance use causes change in the structure and synaptic connections in the brain (Volkow & Li, 2004). These impairments are exacerbated in those with more servere SUD (Volkow, Fowler, & Wang, 2003).

A systematic review conducted by Fernandez-Serrano, Perez-Garcia, and Verdejo-Garcia, (2011) found both substance-specific and generalized substance use disorder-related cognitive deficits. This systematic review used peer-reviewed studies from the PubMed and PsycInfo databases, investigated both specific and generalized cognitive impairments and differentiates between pure and poly-substance studies. Results from mono substance users of particular interest with results reported in Table 2.

Table 2

Cognitive impairment effect sizes in mono substance users adapted from Fernandez-Serrano, Perez-Garcia, & Verdejo-Garcia, 2011

Cognitive impairments	Cannabis		Cocaine		Methamphetamines		MDMA		Heroin		Alcohol	
	n	*d*	*n*	*d*	*n*	*d*	*n*	*d*	*n*	*d*	*n*	*d*
Episodic memory	1	**2.31**			1	**0.87**	2	**1.04**	1	0.48	3	0.35
Semantic memory	1	**3.00**					2	**0.50**				
Selective attention *							1	**1.40**			2	**0.83**
Sustained attention							1	**0.51**			1	**1.03**
Updating fluency							2	**0.63**			1	0.05
Updating reasoning	1	0.39							1	**0.71**	1	0.10
Updating working memory							2	0.40	1	**0.53**	2	0.28
Psychomotor functioning							2	**0.96**			2	0.74
Spatial processing	1	**1.20**					1	**0.58**			1	0.84
Cognitive flexibility*							1	0.35			3	0.45
Impulsive actions*					1	**0.82**	1	**0.54**	1	0.27	3	0.49
Impulsive choice*											1	0.17
Decision making*			2	**0.63**			1	0.27	1	3.8	2	0.26

Note: n = number of studies used to calculate the mean effect size. *d* = mean effect sizes (Cohen˘ıs d). bold: Mean effect sizes reaching at least a moderate magnitude (mean Cohen˘ıs d ≥ 0.5) across studies. * = Impairments of interested to this study. Mean effect sizes were reported regardless of the statistical significance (p-value) of the results reported in original studies.. Blank cells relate to conditions where no data was available for meta-analysis.

While there are a number of other deficits, of particular relevance to the current study are impairments with executive control, which are common across substance type. Deficits in selective attention were found in MDMA and alcohol studies with effect sizes of moderate magnitude. Two studies assessing cannabis and heroin polysubstance found impairments in selective attention as well (*g = 0*.15; Fernandez-Serrano et.al., 2011). Impulsive action and choice overactive in SUD. Evidence shows moderate effect sizes for impulsive action in methamphetamine and MDMA populations, impairments present in heroin, and alcohol populations as well (Table 2). Impulsive choice impairment was present in alcohol populations. Fernandez-Serrano et.al (2011) found moderate magnitude effects between both cocaine and MDMA populations and decision making, with impairments also present in heroin, and alcohol populations (Table 2). Mackillop, Amlung, Few, Ray, Sweet, & Munafo, (2011) found impairments in decision-making to be present in cocaine populations (See Table 6) however there is a gap in the literature exploring pure psychosocial interventions (Fernandez-Serrano et.al., 2011). Alcohol and MDMA studies found deficits in cognitive flexibility (Table 2). Two studies assessing cannabis and heroin polysubstance found impairments in cognitive flexibility as well (*g = 0*.38).

Impairment effects on treatment outcomes

Psychosocial therapies uses a range of cognitive-based treatments such as CBT and MET and are considered best practice for a range of use disorder types (Acosta, Marsch, Xie, Guarino, Aponte-Melendez, 2012; SAMHSA, 2016). However, researchers argue that cognitive deficits may interfere with a treatment seeker's ability to engage in or benefit from these treatments (Lyvers, 2000).

Studies have found strong correlations between cognitive impairment and treatment dropout (Hagen et al., 2017). In particular, cognitive processes that require individuals to regulate, control, and manage craving and drug seeking behaviors are paramount to treatment success. These neurocognitive mechanisms (top-down and bottom-up) make a meaningful contribution to clinical outcomes (Manning el.al., 2017; Fernandez-Serrano, Perrales, Moreno-Lopez, Perez-Garcia, & Verdejo-Garcia, 2012).

Top-down processes are mechanisms that use prior knowledge to interpret contextual information (Freberg, 2010, Manning et. al.,2017), and include executive functions such as decision making, response inhibition, cognitive flexibility and executive control (SAMHSA, 2016). *Bottom-up processes* are mechanisms that control automatic and impulsive processes (Freberg, 2010), including spontaneous memory association, attentional and approach bias toward substance-related stimuli (SAMHSA, 2016). As outlined previously, impairments in these areas have shown to be present in SUD populations (Fernandez-Serrano et.al., 2011) and linked to lower treatment retention (Manning, et. al.,20172017).

Manning et. al. (2017) proposes that poor treatment outcomes may be associated with a combination of overactive bottom-up processes and underactive top-down processes. The theoretical framework proposed is shown in Figure 2.

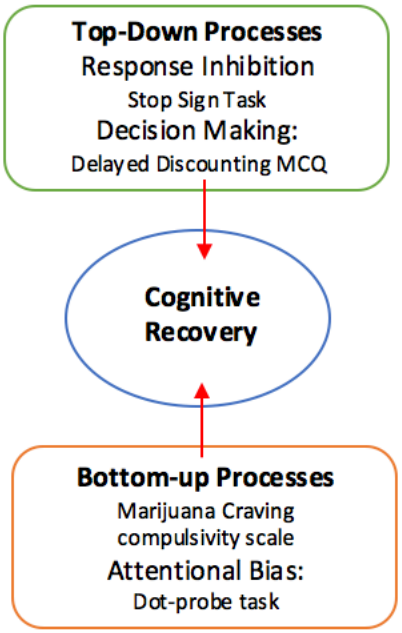


***Figure 2*:** Theoretical framework proposed by Manning el.al.(2017) adapted for the purposes of the study.

Bottom-up Mechanism: Attentional Bias

Evidence suggests hypersensitization of the meso-cortico-limbic reward pathways which drives incentive motivation (i.e. 'wanting') is responsible for this enhancement in bottom-up processes (Robinsone, & Berridge, 2000). Neuroimaging studies have found a reduction in hypersensitivity in this circuit when treatment is successfully implemented (Zilverstand et al, 2016). Hypersensitization is caused by strong classical and operant conditioned responses, as drug related stimuli are repeatedly paired with urge-related responding (Copersino, 2017). Prolonged drug use strengthens these associations, leading to cognitive biases toward substance related stimuli, making abstinence difficult (Copersion, 2017).

A meta-analysis of 69 studies found bottom-up processes to be associated with craving although demonstrate a small magnitude effect (r=.19; Field et al, 2009). Bottom-up processes (cognitive bias) have also been associated with relapse and show a medium effect size (89 studies, r=.31; Rooke et. al., 2008). One aspect of cognitive bias presented in bottom-up processes is attentional bias. Attentional Bias refers to the automatic and subconscious attention, dependent individuals give to drug related stimuli over non-drug related stimuli (Sofuoglu, et. al., 2013). This cognitive mechanism has been associated with impulsivity (Nuijten, Blanken, Brink, Goudriaan & Hendriks,2016) and craving (Cox, Hogan, Kristian, & Race, 2002) and may contribute to associations found between attentional bias and relapse (Field & Cox, 2008, Sofuoglu et.al., 2013). A common way to assess this bias is through the use of the dot-probe task. The dot-probe task has links to prolonged attention and drug craving (Field & Coxs, 2008). Subjects are given a fixation point, presented with two stimuli which are subsequently removed, and then are then presented with a probe placed in the position that one of the stimuli had occupied previously (Figure 3). Reaction times to probes that replace substance-related stimuli are compared with those that replace neutral stimuli.

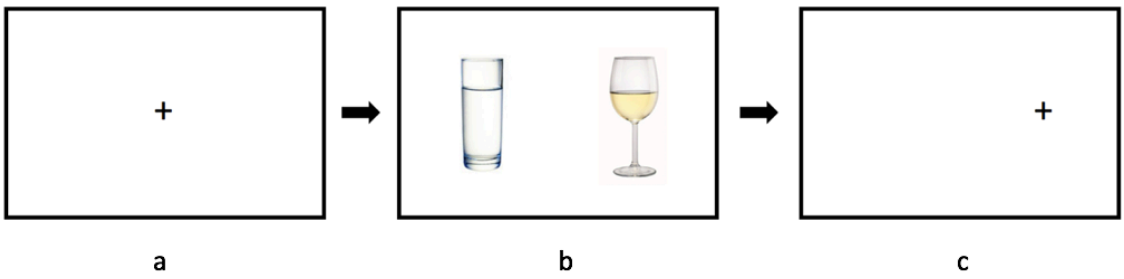


***Figure 3*:** Bottom-up Attentional Bias Dot-probe task. a) fixation point. b) paired neutral with drug stimuli. c) response probe.

Substance-related stimuli are responded to much more rapidly than carefully matched neutral stimuli, therefore attentional bias for substance-related cues is inferred (Field, Munafo, & Franken, 2009). Evidence suggests greater attentional bias to be negatively correlated with severity of substance abuse (Field, Moog, Zetteler, & Bradley, 2004). Effect sizes for studies using the dot probe task or visual probe task (where the probe is a symbol instead of a dot) are shown in Table 3. Small to medium effect sizes can be seen using the dot-probe task to measure attentional bias in substance use disorder populations.

Table 3

Characteristics of studies using the dot probe task or visual probe task to measure Attentional Bias and Main effect sizes correlation with SUD severity.

Author	*N*	Substance	Task	N of paired stimuli	Length of presentation (ms)	*r*	*SE*
Field, Eastwood, Bradley, and Mogg (2006)	45	Cannabis	VP	18	2000	.24	.15
Field et. al. (2004)	40	Alcohol	VP	14	Varied between 200, 500, & 2000	.41	.16
Lubman, Peters, Mogg, Bradley, and Deakin (2000)	32	Heroin	DPP	-	500	.35	.19
Townshend and Duka (2001)	32	Alcohol	DPP	20	500	.37	.19
Townshend and Duka (2001)	32	Alcohol	DPW	10	500	.06	.19

Note: DPP= Dot Probe using pictures, DPW= Dot Probe using words VP= Visual Probe

Literature suggests that attentional bias may be a cognitive marker for treatment dropout in cannabis population (Field, Marhe, Franken, 2014). Associations between attentional bias and treatment outcomes are mixed (Leeman,

Robinson, Waters, & Sofuoglu, 2014). A study by Carpenter, Schreiber, Church and McDowell (2006) found greater attentional bias to cocaine stimuli to be associated with poorer treatment outcomes. On the other hand, study conducted by Capenter, Martinez, Vadhan, Barnes-Holmes, & Nunes (2012) found stronger attentional bias to cocaine stimuli to be correlated with greater treatment attendance rates ($r = .51$, $p = < .05$) and a greater proportion of cocaine-free urines ($r = .49$, $p = < .05$). Many studies assessing attentional bias, including those with positive findings (eg. Table 3) are underpowered and have been criticised for having methodological weaknesses and inconsistencies (Christiansen, Schoenmakers, & Field, 2015). Underpowered studies can yield false positive or null findings (Button et al., 2013). Christiansen, Schoenmakers, and Field (2015) calls for standardised testing to be used, therefore this study will be modeled closely after their recommendations.

Top-down Measure: Response Inhibition

The theoretical framework underlying the cognitive mechanisms present in addiction show a constant tension between top-down (self-control) and bottom-up (urge-related) responding (Copersino, 2017). In contrast to the unconscious nature of bottom-up processes, top-down processes include high-order cognitive functioning such as metacognition and executive functioning (Copersino, 2017). Manning et.al. (2017) proposes diminished top-down processes to be predictive of poorer treatment outcomes and relapse. Drug related impairments to both the functioning of the dorsolateral prefrontal cortex (responsible for goal-directed behaviour) and orbitofrontal cortex (responsible for processing information about environmental contingencies) are attributed to diminished top-down/executive responding (Sofuoglu el.al., 2013).

The two most widely recognised components of neurocognitive impulsive behaviour are impulsive action and impulsive choice, the ability to control these urges are important for treatment success (Rupp el.al., 2016). Response inhibition refers to the ability to exhibit control over impulsive actions and is a strong predictor of treatment completion (Stevens, Goudrian, Verdejo-Garcia, Roeyers, & Vanderplasschen, 2015). The ability to withhold or stop a behavioural response and transition to a more appropriate behaviour is an important mechanism in overcoming SUD. As previously highlighted, impairments in response inhibition have been seen in SUD populations (Table 2). These impairments are also a criterion for substance use disorders in the DSM-5 (American Psychiatric Association, 2013), with the first four criterion focusing on a person's difficulty to control/reduce drug use (see Table 1). Response inhibition is often assessed via tasks such as the Stop-Signal Task (SST). In the SST, participants are prompted to respond to stimuli in a two-alternative forced choice task, with a stop-signal presented very occasionally and at varying intervals after stimulus onset prompting participants to withhold their response after it has already been initiated (Figure 4).

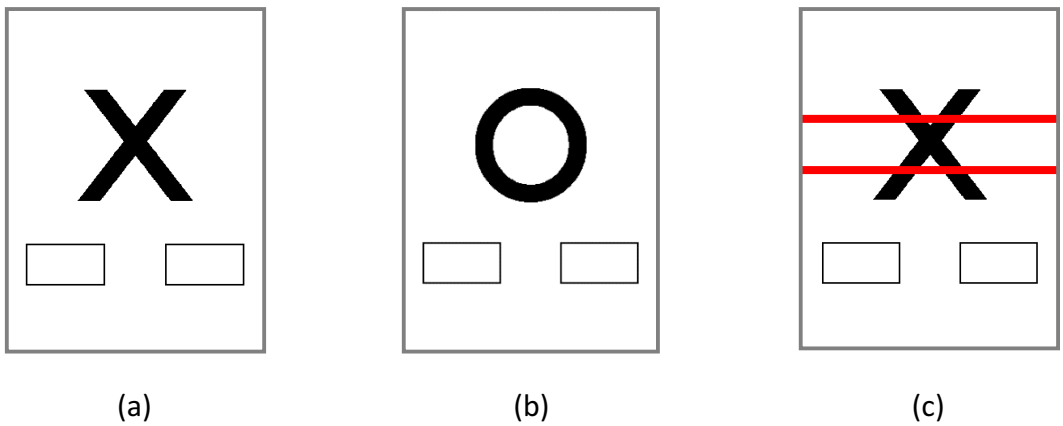


Figure 4: Top-down Response Inhibition Stop Signal task. a) left response. b) right response. c) left response followed by stop signal, presented initially 250ms and increasing or decreasing at 50ms intervals following correct or incorrect responses.

Poor performance in this task has shown associations with relapse and treatment drop-out in substance dependence, including cocaine (Fernandez-Serrano et.al.,2012), alcohol (Li, Luo, Yan, Bergquist, & Sinha, 2009) and methamphetamine (Monterosso, Aron, Cordova, Xu, & London, 2005). Evidence to suggest this task is associated with severity of SUD is also evident (Fernandez-Serrano el.al.,2012). Although clinical literature suggests cognitive impairments and poor inhibitory control are linked to drug treatment outcomes, studies reveal mixed results, as shown in Table 4. Significant associations have been found between all illicit drugs included with small to moderate effect sizes, with the exception of cannabis.

Table 4

Weighted mean effect sizes (g) from meta-analysis conducted by Smith, Mattick, Jamadar, & Irsdale (2014) for stop signal task when compared to control group.

Substance	*k*	*g*	SE	95% CI	*z*	*p*
Cocaine	9	0.464	0.08	0.29-0.64	5.24	<.001
Methamphetamine	3	0.724	0.18	0.36-1.09	3.92	<.001
Alcohol	6	0.395	0.09	0.23-0.56	4.61	<.001
Cannabis	6	0.004	0.12	-0.23-0.24	0.04	.971

Note: *k* = number of studies, SE = standard error.

Impairments in decision making have also been seen in SUD populations (Table 2). Impulsive decision making is of particular interest to behavioural economics as it aims to understand choice behaviour under conditions of constraint (Mackillop et.al., 2011). The delayed Discounting task (DD), tests components of impulsive choice behaviour (Stevens, Verdejo-Garcia, Roeyers, Goudriaan, & Vanderplasschen, 2014) as it assesses an individual's preference for immediate over delayed rewards. The task gives participants an option between a hypothetical monetary reward now or a larger reward after a delay period. Monetary rewards are

between $11-85 with the delay being between 7-186 days. For example, “would you prefer $54 today, or $55 in 117 days?”. Meta-analysis has found DD to be associated with severity of substance use (Yi, Mitchell, & Bickel, 2010). A meta-analysis showed, when compared to control groups, participants with SUD preformed poorer (Mackillop et al, 2011). Table 6 shows results of the meta-analysis conducted by Mackillop et al, (2011) with small to medium effect sizes across studies.

Table 6

Results of Meta-analysis conducted by Mackillop et al, (2011) showing comparisons of delayed discounting between SUD population (in-patient and out-patient) and control group.

Sample	*k*	*d*	Z	*p*
Overall Sample	57	0.58	17.17	<.0001
Inpatient Studies				
Alcohol	9	0.50	5.87	<.0001
Stimulant	6	0.87	6.78	<.0001
Opiate	3	0.76	5.57	<.0001
Cannabis	1	0.20	0.71	.480
Outpatient Studies				
Alcohol	5	0.26	2.11	<.05

Note: Overall sample included tobacco (17), gambling (7), & mixed

Fewer studies have explored the relationships between DD and early-dropout rates, with much focus on DD as a predictor of relapse (Peters, Petri, LaPaglia, Reynolds, & Carroll, 2014; Stevens el.al., 2014). Studies which show significant associations between DD and treatment outcomes are represented in table 7.

Table 7

Standardised coefficients (β) and characteristics of studies using a delayed discounting task to treatment outcomes.

Studies	N	*Substance*	*k* value	Outcome Measure	ß
Peters et.al. (2014)	127	Marijuana	Overall	Percent days of marijuana abstinence at follow-up (12 months)	.01
Stevens et.al. (2015)	84	Any	In overall	Still in Inpatient treatment at 1 month	-4.50
Stranger et.al. (2014)	165	Marijuana	In overall	Continued abstinence at 1 month	-.020
Passetti et.al. (2010)	48	Opioid	Logistic	Still in treatment (3 months)	-3.33

Relapse rates may be a by-product of treatment engagement, therefore exploring relationships between DD and early-dropout rates may bridge a gap in the literature and lead to further insight into how one should conduct interventions. Given that out-patient therapy is largely based around cognitive behaviour therapy and goal setting, the ability to choose long term progress rather than immediate gratification is necessary for therapy success. Individuals who drop-out of treatment after less than 3 months, have been shown to have a higher likelihood of choosing immediate rewards (Stevens el.al, 2015).

Other Predictors of Treatment drop-out

There has been much research into individual factors contribute to relapse rates in out-patient talk-based therapy (Turner, LaRowe, Horner, Herron, & Malcome, 2009; Stevens et.al., 2015), but there is a lack of an overarching theoretical framework. A systematic review conducted by Brorson, Arnevik, Rand-Hendriksen & Duckert (2013) identified a large number of correlates of dropping out from addiction treatment, including several patient factors such as younger age,

female gender, lack of motivation, lower education and lower socioeconomic status. Brorson et al (2013), also identified treatment factors such as the treatment setting (residential or out-patient), non-pharmacotherapy, court mandated treatment, program duration and therapist qualities. SUD has also been associated with higher self-reported measures of trait impulsivity (Li et al., 2006; Monterosso et al., 2005). A study by Stevens et.al. (2015) however, found when compared to trait impulsivity, impulsive behaviour was a better predictor of treatment relapse.

Many factors associated with treatment outcomes of SUD are correlated with each other. Samuel, Carroll, Canning-Ball and Rounsavillle (2006) found trait impulsivity and treatment readiness to be significantly associated with early treatment drop-out (first month). Treatment drop-out in SUD populations have also found to be associated with impulsivity (Nuijten et.al.,2016) and craving (Cox et.al., 2002). As both the DD and SST are recognised components of neurocognitive impulsive behaviour, it is logical to suggest trait impulsivity to be a potential factor in treatment engagement and early dropouts. As previously stated, both components have shown to be strong predictor of treatment completion (Stevens et.al., 2015).

SUD and depression and anxiety show a high comorbidity, with studies showing significant negative impacts of these affective disorder and both symptom severity and treatment outcomes (Lubman, 2015; Brorson et al, 2013). Wills and Hirky (1996) propose that SUD may be a coping mechanism for psychological distress. Literature surrounding the comorbidity of depression and substance abuse is lacking in adult populations and results are mixed. Some studies show an association between depression, substance abuse and cognitive impairments (Lubman, 2015). However, Pencer & Addington (2003) found in a sample of

individuals with comorbid depression and mild-to-moderate substance abuse disorders, participants did not exhibit more cognitive impairment than those who are diagnosed with just depression. Evidence also shows associations between personality disorders and early treatment drop out (Brorson et al, 2013).

It is difficult to assess the underlying causes of treatment drop-out in SUD. There is a wealth of literature into individual factors associated with poor treatment outcomes, however a lack of overall synthesis. Studies that show strong correlations between a specific factor (e.g. psychological distress, impulsivity, cognitive deficits) and treatment outcomes often fail to control for other potential factors that have shown to be correlated with outcome. Mixed results between studies assessing cognitive deficits and treatments outcomes may be due to a lack of comprehensive control for other predictive factors.

This Study

This study aims to better explore the relationship between relapse rates and cognition. It aims to compare cognitive assessments that have been associated with treatment outcomes, in particular, attentional bias via a dot probe task (a bottom-up process), response inhibition via a stop signal task and decision making via a delayed discounting task (top-down processes) as predictors of treatment outcome. This study's primary hypothesis is that poorer performance in these cognitive tasks (greater substance use attentional bias, poorer inhibitory control, and greater emphasis on short term outcomes) will be associated with poorer treatment engagement (less attendance) at one-month follow-up, thus consistent with the theoretical framework proposed by Manning et.al. (2016). In addition, this study will

explore the severity of substance abuse disorder as a correlate of these cognitive measures, as this is also a key proposal underlying the Manning et al (2016) model. The secondary hypothesis is that participants who have more symptoms of substance use disorder will show poorer performance on these cognitive tasks.

Method

Participants

Experiment one: Cognition in Treatment (CTx) Study

Seven participants were recruited: Four experiencing problems with alcohol, and one each with cannabis, opioids, and methamphetamine. All were outpatients currently in 'talk-based' treatment for substance use problems; exclusion criteria are summarised in Table 8.

Recruitment occurred via advertisements placed at drug treatment services across Hobart (Holyoake, Anglicare, The Link Youth Health Service, Salvation Army Bridge Program, Alcohol and Drug Services). Participants responded to advertisements by either completing a screening survey online or via telephone. Participants reimbursed $40 to compensate for time and out-of-pocket expenses. Ethical approval was provided from the Tasmanian Social Sciences Human Research Ethics Committee (#H0017170; See Appendix C for full report).

Table 8

Exclusion criteria for Experiment 1 and 2

Exclusion Criteria	Ex1	Ex2
Under 18 years	*	*
Non-English speakers	*	*
Pharmacotherapy for substance problems (e.g. methadone)	*	*
Inpatient treatment	*	*
Current medical/inpatient withdrawal for substance use	*	
Presence of comorbid licit or illicit SUDs (nicotine or caffeine not included)		*
First time in treatment		*
Court mandated to attend treatment		*
Pregnant/lactating females		*

Experiment 2: Sativex Trial

Due to difficulties with recruitment, existing data from 67 participants randomised to the placebo group for a trial of nabiximols (Sativex®) for cannabis use disorder (Bhardwaj et al., 2018) were analysed to investigate the hypotheses. Participants were recruited from four addiction medicine centers in New South Wales. Participants were aged between 18 and 65 years old, seeking treatment for cannabis use disorder, and had not responded to at least one prior attempt at treatment for their cannabis use. Exclusion criteria presented in Table 8. Participants were recruited through referrals from drug and alcohol treatment services, media advertisements and the University of Sydney website. Ethical approval was provided by the Human Research Ethics Committee of South East Sydney Local Health District (HREC/14/POWH/701).

Materials

Table 9

Measures used to operationalise the constructs in the two studies

Construct	Experiment 1: CTx	Experiment 2: Sativex
Bottom-up drive strength	Attentional bias dot probe	Marijuana Craving Compulsivity Scale
Top-down inhibitory processing	Stop Signal Task Delayed Discounting MCQ	Stop Signal Task
Consumption of target drug	Timeline Follow-back	Timeline Follow-back
Substance use disorder symptoms	AUDAIS-5	CPQ
General cognitive function	MOCA WTAR	WTAR
Psychological distress	Kessler 10	DASS
Readiness to change	SOCRATES	
Trait Impulsivity	Eysenck I7 Impulsivity BIS/BAS Reward	
Treatment Outcomes	Still attending treatment at week 4	Still attending treatment at week 4 and 12

Operationalisations of bottom-up drive strength

Attentional bias dot probe (DP). This was modelled after Miller and Fillmore (2010). Participants are required to quickly identify the location of a probe target (left or right). The probe is presented in one of two locations that have just had substance use-related or matched neutral stimuli presented. Ten substance use stimuli were paired with 10 neural stimuli which looked similar in structure, e.g. beer paired with soft-drink (See Appendix D for stimuli). Substance use stimuli were chosen to relate to the participant's problem substance (amphetamines, cannabis, alcohol or opioids). When compared to general drug paraphernalia (syringe, lighter, spoon etc.) internal reliability is higher when stimuli are personalised to an individual's main substance of concern (Christiansen, Mansfield, Duckworth, Field, & Jones, 2015).

All pictures were presented four times, for a total of 80 trials. A fixation point of 500ms begun each trial, followed by 1000ms of the paired items at the left and right of the screen. An arrow probe followed and presented either at one of the stimuli locations, with these locations counterbalanced. It remained on the screen for a max of 1000ms until the participant responded to the direction of the probe. Attentional Bias was calculated in milliseconds using the mean of Dot Probe Reaction Time (DPRT) for incongruent trials (probe and neutral stimuli same position) and congruent trials (probe and drug stimuli same position).

Marijuana Craving Compulsivity Scale (MCQ). The MCQ assesses four aspects of cannabis craving (compulsivity, emotionality, expectancy and purposefulness) on a 7-point Likert scale, from 1 = strongly disagree to 7 = strongly agree. The seven item compulsivity subscale was chosen as a proxy for bottom-up drive, as the content of these items reflect the automatic, stimulus driven nature of bottom-up processes (See Table 10). The MCQ has shown to be a valid and reliable test of compulsivity in marijuana use populations (r=.82; Heishman, Singleton, & Liguori, 2001).

Table 10

MCQ Compulsivity factor structure.

Item	Factor Loading
If I smoked a little marijuana right now, I would not be able to stop using it.	0.59
I would do almost anything for a joint.	0.55
It would be difficult to turn down a joint right this minute.	0.50
Starting now, I could go without smoking marijuana for a long time.	0.40
I would not be able to control how much marijuana I smoked if I had some here.	0.64
I could easily limit how much marijuana I smoked right now.	0.63
I do not need to smoke marijuana right now.	0.72

Operationalisations of Top-Down Inhibitory Processing

Stop Signal Task (SST). This tests participant reaction time in response to target stimuli in a two-alternative forced choice reaction time paradigm. Participants were instructed to touch a left or right square as quickly as possible in response to a visually presented letters X or O, respectively. Occasionally there was a stop signal presented (~~X~~) after a short delay following stimuli presentation. Timing between the first trial and the stop signal was 250ms, with the following trials increasing or decreasing by 50ms depending on response correctness. Stop signal reaction time (SSRT) was recorded as the measure of response inhibition. The SSRT is defined as the minimum delay in which participants can inhibit their response to stop signals 50% of the time (calculated by subtracting stop signal delay from the mean go signal reaction time). This task included a starting fixation point of 500ms and ran 48 trials with 25% being stop signal trials.

Delay Discounting Task (DD). Created by Kirby, Petry, and Bickel (1999), the DD (27 questions) used a monetary choice questionnaire to assess delay discounting. Questions consists of a choice between an amount of money now or a larger amount later. Monetary rewards ranged between $11-85 with delay ranging between 7-186 days. For example, "would you prefer $54 today, or $55 in 117 days?" The Mazur, 1987 hyperbolic discounting model was used to calculate overall rate of discounting and produce a k value for each monetary group and one based on participant's overall responses. The k values are calculated using the formula, $V = A1+kD$ (V= magnitude of the immediate reward, A= magnitude of the delayed reward, and D= length of the delay for that item). In differentiating between patients with heroin dependence and control subjects, the MCQ has demonstrated strong construct validity (Kirby et. al., 1999).

Covariates

Timeline Follow-back (TLFB). The TLFB *(Sobell and Sobell, 1992)*, asks participants to provide self-reported information regarding their days of substance use in the month prior to assessment. It provides a systematic recall-supporting framework to support individuals to retrospectively recall patterns, quantitative measures and variability of substance use over the past 28 days. A systematic review found when compared to biological samples, TLFB validly detects use of illicit substances in populations with SUD between r=.72 to r=.85. (Hjorthoj, Hjorthoj &Nordentoft, 2012).

Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5). The AUDADIS-5 is a standardised structured approach to identify SUD criteria in concordance with the DSM-5 (Hasin et al, 2015), designed for application in epidemiology surveys. The questions are used to assess the presence of SUD criteria in the 12 months prior to interview. The measure has demonstrated good to excellent validity (Duresso, Matthews, Ferguson, & Bruno, 2016).

Cannabis Problems Questionnaire (CPQ, Copeland, Gilmore, Gates, & Swift,2005). The CPQ is a 27 item scale with responses scored on a 11-point Likert scale (0 = doesn't apply to me to 10 = strongly apply to me). The CPQ measures acute and physical, psychological, and social consequences of cannabis use. Significant positive correlations were found between total CPQ score and the number of DSM-IV SUD symptoms in cannabis consumers (r= .72; Copeland, Copeland, Gilmour, Gates & Swift, 2005).

Wechsler Test of Adult Reading (WTAR). The WTAR consists of 50 words that have irregular grapheme-to-phoneme correspondence. Participants are asked to read these words aloud and the correctness of each pronunciation is recorded. The WTAR was co-normed with the Wechsler Adult Intelligence Scale 3rd Edition and provides a close estimate to these IQ values (r = .84; Green et. al., 2008).

Montreal Cognitive Assessment (MOCA). The MOCA is a brief screening tool for cognitive impairment, assessing domains of attention, concentration, executive functions, memory, language, visuospatial ability, conceptual thinking, calculations, and orientation, with a total score of 30. It has been been widely used and validated as a screening tool for cognitive problems in substance dependent populations (Marceau, Lunn, Berry, Kelly, & Solowij, 2016).

Kessler-10 (K10, Kessler, Andrews, & Colpe, 2002). This assesses psychological distress, and consisting of 10-items scored on a 5-point Likert scale (1= None of the time to 5=All of the time) asking the participant to rate symptoms in the past 4 weeks. Each item is therefore scored out of five with the maximum score being 50, indicating severe distress, and the minimum score is 10, indicating no distress. The scale has been well validated in SUD populations. In a validation study of the K10, more than 90% of an Australian general population sample scoring more than 30 on the K10 met criteria for an ICD-10 disorder (Andrews & Slade, 2001).

Depression, Anxiety and Stress Scale Short-form (DASS, Lovibond & Lovibond, 1995). The DASS is a 21 item questionnaire using a 4-point Likert scale (0= does not apply to 3= applied to me very much), assessing severity of depression,

anxiety and stress. Depression and anxiety scores were used given the conceptual relationship with psychological distress assessed in the K10. The DASS21 depression scale demonstrated a correlation of 0.79 with the Beck Depression Inventory and the DASS 21 anxiety scale has a correlation with 0.85 with the Beck Anxiety Inventory in a clinical sample (Antony et al, 1998)

Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES, Miller & Tonigan, 1996). This is a 19 item scale assessed with 5-point Likert items (anchors strongly disagree; strongly agree). It is designed to assess readiness to change in those with substance dependence and consist of three factors, recognition, ambivalence and engagement to change, reflecting the transtheoretical model of Prochaska and DiClemente (DOH, 2004). High positive correlations have been identified between baseline measures of SUD and ambivalence (r = .88), recognition (r = .96), and Taking Steps (r = .94; Williams & Tonigan, 1996).

Eysenck Impulsivity Subscale (I7; Eysenck, Pearson, Easting, & Allsopp, 1985). The 17 is a subscale of the Eysenck's Impulsivity Inventory which measures personality traits of impulsivity, venturesomeness, and empathy. The 19 item subscale scale focus on impulsivity and requires yes/no (coded 1 & 0) response. Maximum score on the scale is 19, with higher scores indicating higher levels of trait impulsivity (validity). The 17 has shown to hold both cross-cultural validly and generalisability across sexes (Russo, Leone, & Pascalis, 2011).

Procedure

Experiment 1 (CTx):

Participants were tested at 1.5hr sessions at the Psychology Research Centre at the University of Tasmania. Participants were screened for eligibility though an online survey. Demographics and all scale scores were collected in an online RECDAP database (Table 11). The cognitive tests were conducted using Inquisit web (offline) on iPad and Penscreen software on android tablets. Batteries were conducted in standardised order. A follow up phone call to participants was also conducted 4 weeks from date of initial treatment. Participants were asked if they were still attending sessions at their service provider.

Table 11

Order of Experimental 1 procedure

n	Measure	Data collection method
1	Informed Consent for Baseline, 1 month and 3 month follow-up	Manual
2	Demographics and Baseline craving	REDCAP
3	Time Line Follow Back	REDCAP
4	Drug Q-score	REDCAP
5	AUDADIS-5	REDCAP
6	Cued Craving	REDCAP
7	WTAR	REDCAP
8	Cognitive battery 1: Dot Probe Task * Iowa Gambling Task Emotional Stroop	Millisecond software
9	Delay Discounting Task *	REDCAP
10	Cognitive battery 2: Go no Go Flankers N Back Stop Signal Task*	PenScreenSix Cognitive Testing Software v1.6
11	MoCa	REDCAP
12	SOCRATES	REDCAP
13	K10	REDCAP
14	Eysenck 17 Impulsivity Scale	REDCAP
15	BIS/BAS Scale	REDCAP

Note: * Cognitive measures used in this study

Experiment 2 (Sativex)

Participants were receiving placebo in a 12-week drug trial. All participants also received individual counselling over this period, consisting of CBT, withdrawal management and relapse prevention with participants required to attend a minimum of two sessions. All participants also received followed-up research interviews, at 4 and 12 weeks. Retention at each of these time points was used as the outcome measure for this study. Full study protocol can be found in Bhardwaj et. at. (2018).

Design

A correlational design was employed for both experiments. Due to sample size, only correlations were conducted in the CTx study. For analysis of the Sativex trial data both Pearson correlations and hierarchical linear regression models were used to test the first hypothesis (whether cognitive measures are associated with SUD severity). Hierarchical logistic regression models were also conducted with Sativex trial data to examine the second hypothesis (whether cognition is associated with treatment outcomes). The outcome variables were dependence (indexed by CPQ) and treatment drop out (by week 4 or by week 12). Independent variables were SST RT and MCQ compulsivity. SST RT data was examined for outliers, and two participants reported extreme scores (>2SD from group mean), both of whom also had extreme dependence scores. However, when these participants were removed from analyses, no substantial differences were identified in results so these participants were retained. Analyses with removed participants are available in Appendix F. Power analysis estimates based on these hierarchical linear regression models to provide a R^2 of 0.1-0.2, required a minimum of 52 participants for reliable (power=.80) identification of a statistically significant effect (α =.05).

Results

Experiment 1: CTx

Seven participants, with a mean age of 41.7 (range 25-61) were included. Participants were experiencing AUDADIS-5 assessed moderate to severe SUD with a mean DSM-5 symptom count of 7.7 out of 11 (range = 4-10).

Pearson correlations identified no statistically significant correlations between cognitive performance, and severity of dependence or any covariates (Table 12). Results revealed all relationships were non-significant. Bottom-up drive (DPRT) showed a weak negative linear relationship with dependence measure. A weak positive relationship was found between SSRT and dependence. A moderate positive relationship was found between DD measure and dependence. DD showed weak negative relationship with WTAR, indicating higher discounting was associated with lower measures of pre-morbid cognition. SSRT showed a weak positive relationship with WTAR and a strong positive relationship with MoCa, both measures of pre-morbid cognition. DPRT showed moderate negative relationships with both ambivalence and trait impulsivity. A moderate positive relationship was found between DD and psychological distress. Weak negative relationships were found between psychological distress and both DPRT and SSRT. Significant positive correlations were also found between dependence and psychological distress ($r = .842$, $p < 05$) and readiness to change ($r = .893$, $p < .01$). Correlations between other covariates are reported in Appendix E.

Table 12

Pearson Correlations between cognition (Top-down Inhibition & Bottom-up Drive) and covariates in experiment 1

Variables	Bottom-Up (DPRT ms incongruent)	Top-Down (SSRTms)	Top-Down (DD log *k*)
	r	*r*	*r*
Bottom-Up (DPRTms incongruent)	-	0.58	0.12
Top-Down (SSRTms)	-	-	0.41
Top-Down (DD log *k*)	-	-	-
Dependence (DSM symptom count)	-0.10	0.29	0.52
WTAR	-0.06	0.31	-0.35
MoCa	0.38	0.66	0.31
Psychological Distress (k10)	-0.29	-0.30	0.55
Readiness to change - SOCRATES recognition	-0.38	-0.26	0.38
Readiness to change - SOCRATES ambivalence	-0.44	-0.05	0.17
Readiness to change - SOCRATES taking steps	-0.36	0.05	-0.21
Impulsivity (I7)	0.45	-0.20	0.21

Note: *p < .05, **p < .01

Bottom-up Drives Attentional Bias Dot Probe relationship with Dependence

Figure 5 shows correlations between dependence and bottom-up measure. The correlation between DSM-5 symptom count and DPRT was r = .29, p = .887. Although not significant, relationship shows a slight positive skew. This could suggest severity of SUD to be positively correlated to attentional bias.

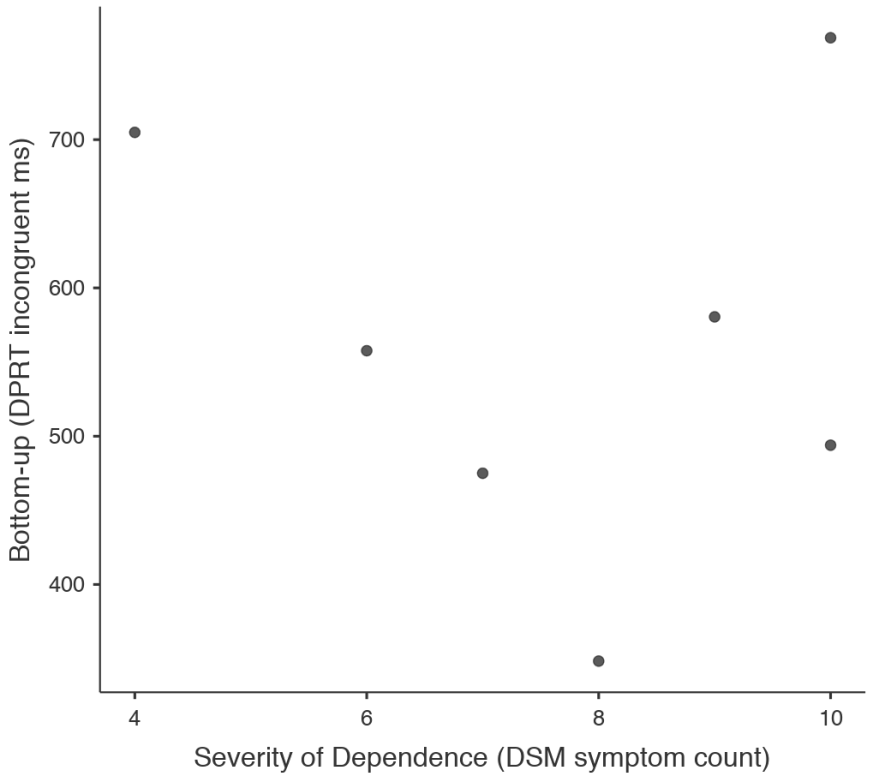


***Figure 5*:** Scatter plot of individual participants Dot Probe and level of dependence

Top-down Inhibition Stop Signal Task (SSRT) relationship with Dependence

SSRT Mean was 515ms (SD=154) with range of scores between 341ms and 708ms. The correlation between DSM-5 symptom count and SSRT was r = .29, p= .587. Visual inferences and correlations were not significant (Figure 6). The two participants with the highest symptom count also indicated slowest response times. Previously. There were no outliers in the data as all SSRT scores fell under 2 standard deviations.

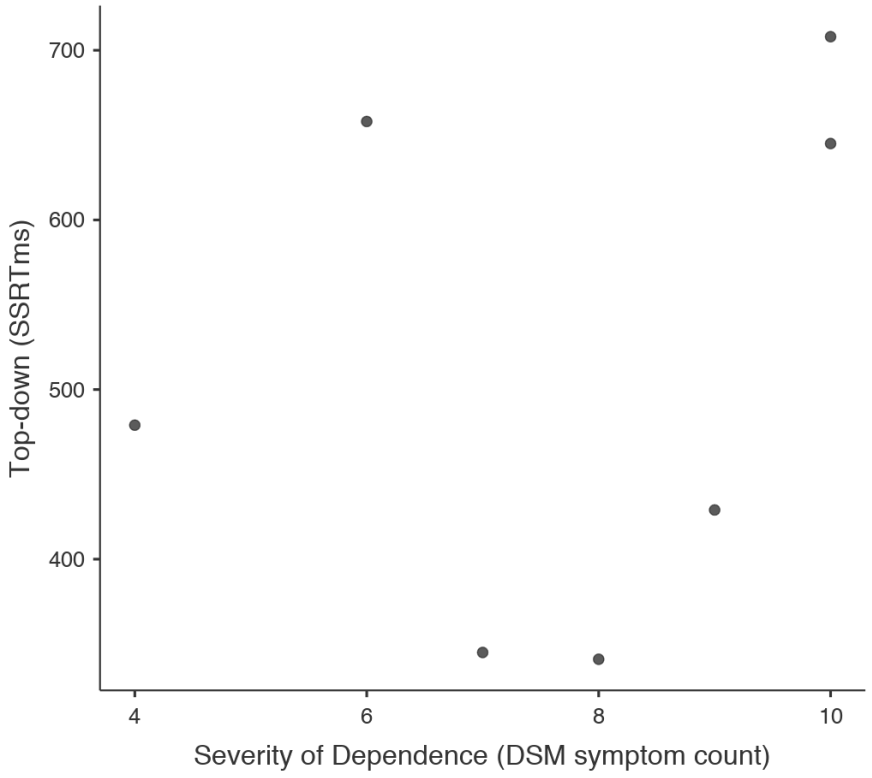


Figure 6: Scatter plot of individual participants SSRT and level of dependence

Top-down Decision Making Delayed Discounting relationship with Dependence

k values for DD task were fitted to a logistic regression following procedures described in Wileyto et. al. (2004) with higher values indicating strong discounting and a preference for immediate rewards. Mean for overall *log k* was 0.03 (SD = 0.03). When running validity checks, to control for malingering, one participant achieved an overall *k* value of 0.00, meaning they consistently chose delayed rewards over immediate rewards regardless of reward size. This participant's data was therefore removed as they did not engage with the task. Correlation between DD and dependence was significant ($r = 0.81$, $p = .049$) upon removal (Figure 6; see Appendix E for all correlations). A significant positive correlation was also found between DD and SOCRATES measure of ambivalence ($r = 0.90$, $p = .037$).

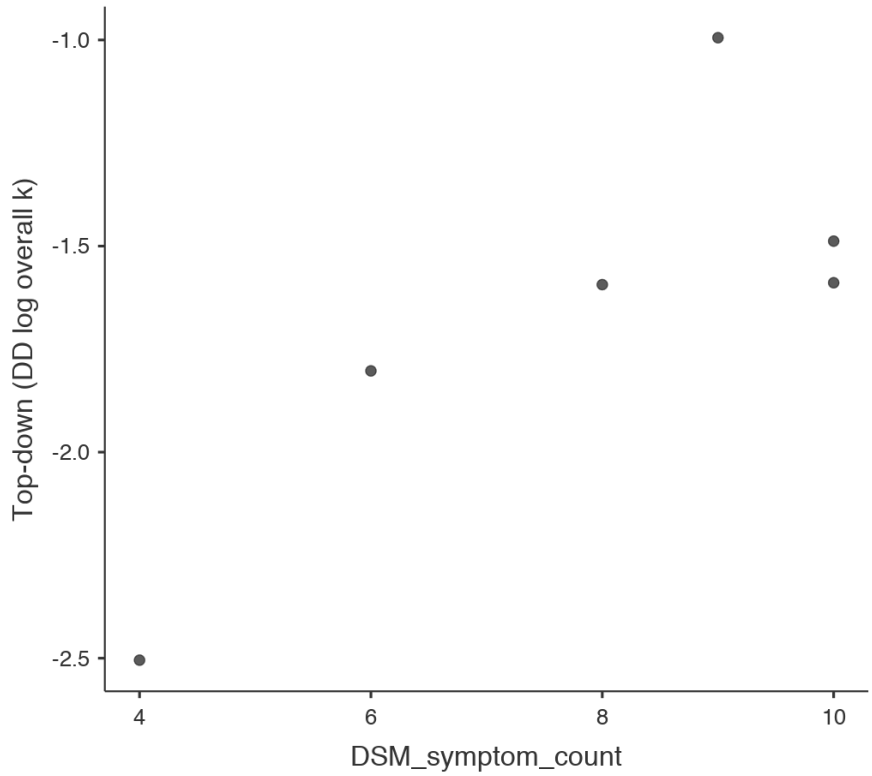


Figure 7: Scatter plot of individual participants Delayed discounting and level of dependence.

Due to difficulties in participant recruitment, and an absence of treatment outcome data, the sample size was small and hence the full set of hypotheses were not able to be examined in the limited time frame of the study. As such, existing data from a large clinical trial (Bhardwaj et al, 2018) was examined to further examine the hypotheses.

Experiment 2

Data from 67 participants (mean age 34.3 years, range 19.8-60.2) was included. As an initial examination of the potential role of cognitive performance and outcomes, participants who dropped out of the trial were compared with continuing participants on their baseline cognitive performance. For very early treatment dropouts (week 4), while non-significant, there were small-moderate magnitude negative differences between those continuing and dropping out (those dropping out had worse SSTRT, Cohen's d=0.36) which smaller when later dropouts were included (by week 12: Cohen's d=0.15). In terms of bottom-up drive strength, while not statistically significant, those that were very early treatment dropouts (by week 4) had compulsivity scores that were greater by a moderate magnitude than those that were retained (Cohen's d=0.33), although this was not retained when later dropouts were included (by week 12: Cohen's d=-0.14).

Table 13

Mean, Standard deviation and Effect sizes for participants still in treatment at week 4 and 12.

Measure		Retained			Dropped out			*t (p)*	BF01	*d*
		M	SD	N	M	SD	N			
Top-down inhibition (SSRT, ms)	Week 4	502.98	119.89	55	546.70	122.20	12	1.14 (.259)	.518	.363
	Week 12	500.70	108.11	30	11.30	5.88	37	0.62 (.541)	.296	.325
Bottom-up drives (compulsivity)	Week 4	9.73	4.73	55	519.00	130.68	12	1.02 (.312)	.467	.151
	Week 12	10.4	4.26	30	9.70	5.48	37	-0.57 (.570)	.289	-.140

One of the key aspects of the theoretical framework is that the extent of top-down inhibitory impairment and bottom-up drive enhancement should be related to the extent of dependence (Table N). There were moderate-small magnitude correlations between both the operalisation of bottom-up drive (compulsivity) and top-down inhibition (SSTRT) and dependence (CPQ; $r = .30$, $p < .01$; $r = -.19$, $p = .109$ respectively). DASS Anxiety was also significantly associated with both dependence and the cognitive measures ($r = 0.31$, $p < .05$ with bottom-up drive; $r = .33$, $p < .01$ with top-down inhibition; and $r = .556$, $p < .01$ with CPQ dependence respectively). Correlations between other covariates used in this study are reported in Appendix F.

Table 14

Pearson Correlations between cognition and covariates in Experiment 2

	Bottom-Up (Compulsivity)	Top-Down (SSRTms)
Variables	r	r
Bottom-Up (Compulsivity)	-	-0.22
Top-Down (SSRTms)	-	-
Dependence	0.31**	- 0.19
Baseline Substance use	0.12	- 0.07
WTAR	- 0.43	0.12
Anxiety	0.31*	-0.33**
Depression	0.18	- 0.20
Readiness to change	0.36**	- 0.28*
Still in treatment week 4	- 0.12	- 0.14
Still in treatment week 12	0.07	- 0.08

Note: *p < .05, **p < .01

To assess the validity of SSRT and control for malingering. Two participants fell under 2 standard deviations below the mean (0.8). Both participants also showed severe dependence scores (195 & 111 out of 297). When omitted from analysis, there was no meaningful difference to the models or correlations, therefore participants were retained. Analysis with low scoring participants removed can be seen in Appendix F. All items of the compulsivity measures were answered, with no missing cases.

Table 15

Hierarchical linear regression of associations between dependence and cognition

	Bottom-UP (Compulsivity)			Top-Down (SSRTms)		
Variable	*t*	*p*	R^2	*t*	*p*	R^2
Model 1			.123			.040
Dependence	2.97	.004*		-1.61	.112	
Model 2			.125			.054
Dependence	2.96	.004*		-1.63	.109	
WTAR	-0.41	.682		0.96	.341	
Model 3			.164			.129
Dependence	1.84	.071		-0.12	.905	
WTAR	-0.57	.572		1.01	.318	
Depression	-0.78	0.44		-0.00	.998	
Anxiety	1.67	.101		-2.13	.037	

Note: * Significant result, $p < .01$.

To further examine whether the theorised relationship between cognitive impairment and severity of dependence symptoms was retained after controlling for potential covariates, a series of hierarchical linear regression models were conducted (Table n). Relevant assumptions of this statistical analysis were tested and met. Collinearity statistics (i.e., Tolerance and VIF) were all within accepted limits, the assumption of multicollinearity was deemed to have been met. Residual and scatter plots indicated the assumptions of normality, linearity and homoscedasticity were all satisfied. Covariates were steadily included in analyses in steps, initially controlling for general cognitive function (WTAR) and then psychological distress (DASS depression and anxiety). Greater bottom up drives were significantly related to dependence after controlling general cognition and fell just short of traditional cut-offs after controlling for psychological distress, thus providing some support for the theoretical framework proposed by Manning et. al. (2017). Contrary to Manning et.

al. (2017), however, strength of top-down drives did not show a statistically significant association with dependence in any of the models examined.

In order to determine whether the proposed theoretical model was predictive of outcome, a set of hierarchical logistic regression models were conducted, whereby it was examined if poorer 'top-down' inhibitory cognition and greater 'bottom-up' drives predicted poorer treatment outcomes (early drop out; Table n). Relevant assumptions of this statistical analysis were tested and met. Collinearity statistics (i.e., Tolerance and VIF) were all within accepted limits, the assumption of multicollinearity was deemed to have been met. All interactions between raw scores and logit had significance values greater than 0.5, indicating that the assumption of linearity of the logit were met.

For both early (by week 4) and later (by week 12) treatment dropout, neither cognitive measure was significantly associated with these outcomes, and the estimates of effect size (R2) were largely trivial or of small magnitude (Table N). While not significantly or meaningfully associated independently with early drop-out, the top-down (SST RT) measure was a statistically significant correlate of week 4 treatment disengagement after controlling for other key correlates of treatment dropout (e.g. psychological distress, baseline use and treatment readiness.

Table 16 *Hierarchical logistic regression of associations between cognition and treatment outcomes*

Variable	Week 4				Week 12			
	Odds ratio	95% CI	*p*	R^2	Odds ratio	95% CI	P	R^2
Model 1				.031				.001
Top-down (SSRT ms)	.991	(0.99-1.00)	.291		1.00	(0.99-1.00)	.813	
Model 2				.025				.000
Bottom-up (Compulsivity)	.936	(0.83-1.06)	.309		1.03	(0.93-1.14)	.564	
Model 3				.085				.003
Top-down (SSRT ms)	.996	(0.99-1.00)	.185		1.00	(0.99-1.00)	.864	
Bottom-up (Compulsivity)	.902	(0.78-1.04)	.153		1.02	(0.91-1.13)	.769	
Model 4				.145				.006
Top-down (SSRT ms)	.997	(0.99-1.00)	.280		1.00	(0.99-1.00)	.821	
Bottom-up (Compulsivity)	.890	(0.77-1.03)	.111		1.02	(0.92-1.13)	.740	
WTAR	.955	(0.90-1.02)	.161		1.01	(0.97-1.04)	.695	
Model 5				.170				.055
Top-down (SSRT ms)	.995	(0.99-1.00)	.196		0.99	(0.99-1.00)	.594	
Bottom-up (Compulsivity)	.901	(0.78-1.04)	.168		1.04	(0.93-1.16)	.544	
WTAR	.960	(0.90-1.02)	.196		1.01	(0.97-1.05)	.554	
Depression	1.035	(0.92-1.17)	.577		0.88	(0.73-1.05	.156	
Anxiety	.880	(0.69-1.13)	.308		1.05	(0.96-1.15)	.279	
Model 6				.390				.097
Top-down (SSRT ms)	.990	(0.98-1.00)	.052 *		0.10	(0.99-1.00)	.471	
Bottom-up (Compulsivity)	.985	(0.82-1.18)	.872		1.06	(0.94-1.20)	.327	
WTAR	.955	(0.96-1.02)	.155		1.01	(0.97-1.06)	.499	
Depression	1.025	(0.87-1.20)	.758		0.90	(0.74-1.08)	.246	
Anxiety	.860	(0.66-1.13)	.278		1.06	(0.95-1.18)	.286	
Dependence	.491	(0.21-1.14)	.097		0.98	(0.94-1.02)	.396	
Baseline cannabis use	.996	(0.97-1.03)	.786		0.99	(0.98-1.02)	.851	
Readiness to change	.956	(0.89-1.03)	.216		0.94	(0.84-1.06)	.319	

Note: * Significant result, $p = .05$

Discussion

The present study was conducted to test the theoretical framework proposed by Manning et al (2017) and examined the relationship cognitive mechanisms (top-down and bottom-up) have, with both severity of dependence and treatment outcomes. Results of the study were mixed, showing some support for the framework proposed.

Manning et al (2017) suggest that the extent of top-down inhibitory control deficits and strength of bottom-up drives should be related to severity of substance use disorder – was this supported?

Associations between bottom-up drives and severity of SUD

Greater bottom-up drives (attentional bias) failed to show statistically significant correlations with severity of dependence in CTx. Participants took longer to respond to neutral stimuli in the presence of drug related stimuli. These results could be due to insufficient power. A relationship may be present in a larger sample size, as scatterplot showed a slight positive skew in data. Previous literature has been criticised for being underpowered and having methodological weaknesses (Christiansen et. al., 2015), and certainly low power was present here. Multiple independent studies have demonstrated a positive relationship between severity of attentional bias and substance use disorder (Field et. al., 2004; Field et. al., 2006; Lubman et. al., 2000, Townshend & Duka, 2001). However, Christiansen et.al. (2015) reviewed the relationship between attentional bias and relapse in a sample of alcohol, cannabis and cocaine users, and found mixed results.

In the Sativex trial, significant positive associations were identified between dependence severity and the bottom-up measure (MCQ compulsivity); however these had small magnitude effect sizes. This magnitude is similar to previous results. Heishman et. al., (2001) found associations between compulsivity and severity of SUD to be trivial in magnitude (r =.18). Compulsivity is an underlying mechanism involved in craving (a criterion for SUD in the DSM-5; Hasin et al., 2013), and is a theoretically valid operationalisation of the automatic, stimulus driven nature of bottom-up processes. These findings provide some support for the theoretical framework under study and indicate a relationship between greater bottom-up drives (compulsivity) and SUD.

Associations between Top-down inhibitory control measures and severity of SUD

Poorer top-down inhibitory control displayed some small to medium significant relationships with SUD severity at baseline. In the CTx a significant strong positive correlation between performance in the delayed discounting task and dependence was apparent, whereby participants with greater number of DSM-5 dependence symptoms had higher discounting scores and a preference for immediate rewards. These results are consistent with previous findings (Yi et. al, 2010; Mackillop et al, 2011) and provides supportive evidence for the proposed theoretical framework.

The SST measure of response inhibition, however, failed to show significant correlations with severity of dependence in either study, contrary to the predictions of the theoretical framework. While poor response inhibition is a criterion for substance use disorders in the DSM-5 (American Psychiatric Association, 2013), a

wealth of research with substance using populations using the SST to operationalise inhibitory control has shown quite mixed results (Li et. al., 2009; Fernandez-Serrano et.al.,2012, Monterosso et. al., 2005). The recent meta-analysis conducted by Smith et. al. (2014) is consistent with the findings here. Very small magnitude and non-significant mean effect sizes were demonstrated for SST when comparing cannabis consumers to controls (see Table 4). Of note, in this analysis, cannabis alone was the only substance that was not associated with a significant SST effect, with significant, small to medium effect sizes apparent for all other illicit drugs studied (Smith et. al., 2014).

However, the absence of an effect may relate to the nature of the SST, particularly as operationalised in the current study. The meta-analysis conducted by Fernandez-Serrano et. al. (2011) demonstrates that response inhibition impairments are clearly present in cannabis consuming populations. Critical reviews of the paradigm have demonstrated that the procedures used to derive the SST RT can have a substantial difference on estimates of inhibitory control from the task (Boehler, Appelbaum, Krebs, Hopf, & Woldorff, 2012) and the methodology applied here was brief (approximately 3 minutes) with limited opportunity for inhibition with only 12 stop signal trials. In previous implementations of this exact paradigm the sensitivity of this task to acute drug-related impairment has been poor, with effect sizes of 0.2-0.3 at breath alcohol levels of 0.05 and 0.08 compared to baseline sober states (Cash, Peacock, Barrington, Sinnett ,& Bruno, 2015).

Manning et al (2017) suggest that the extent of top-down inhibitory control deficits and strength of bottom-up drives should be associated with treatment outcomes – was this supported?

Associations between bottom-up drive measures and treatment outcomes

The second hypothesis aimed to test the predictions outlined by the theoretical framework, whereby poorer 'top-down' inhibitory control and greater strength of 'bottom-up' drives would be associated with poorer treatment outcomes. This was only assessible in the Sativex Trial, and the estimates of variance in treatment outcomes associated with bottom up measures were trivial and non-significant. This is not in line with the proposals of the theoretical framework, and are also contrary to previous literature (Fernandez-Serrano et.al.,2012). Bottom-up measures have shown to be associated with higher relapse rates (Field & Cox, 2008, Sofuoglu et.al., 2013) therefore may also be predictive of poorer treatment outcomes. These associations however, were not found to be significant in this study.

Associations between top-down decision making measures and treatment outcomes

A significant positive correlation was also found between DD and SOCRATES measure of ambivalence. This result is also consistent with previous literature. Stevens et. al. (2014) found a partial mediation between DD and readiness to change. Evidence suggests advantageous decision-making is needed to resolve ambivalence towards drug addiction and treatment engagement (LeBerre, Vabret, Cauvin, Pinon, Allain, & Pitel, 2012).

Associations between top-down inhibitory control measures and treatment outcomes

Measures of top-down inhibitory control (SST) also had trivial and non-significant independent relationships with early treatment dropout. However, the SST has shown to be associated with relapse and treatment drop-out in SUD (Li et. al., 2009; Fernandez-Serrano et.al.,2012, Monterosso et. al., 2005). After controlling for other key correlates of treatment dropout, SST RT was significantly associated with treatment outcomes. Follow up tests revealed when anxiety, and readiness to change were removed from the final model, SSRT was non-significance. As SST is a time pressured task, it is possible that the correlation between the task and anxiety is due the nature of the task itself. However, significant positive correlations were also found between dependence and anxiety, depression and readiness to change. These results therefore could be attributed to suppressor effects in multiple regression. Typically, a suppressor variable is defined as being a variable that is not related to the outcome variable, but due to its relationship with another predictor in the model, improves the overall model fit (Lancaster, 1999). While it is difficult to identify the source of the suppressor effect (Lancaster, 1999), given the statistically significant relationships between SSRT and anxiety, it is possible that this is a key contributor to the effect. Previous literature has found anxiety to be influencial in SUD populations. Comorbidity between SUD and mood disorders are highly prevalent, with studies showing significant negative impacts on both symptoms severity (Brorson et al, 2013) and treatment outcomes (Lubman, 2015; adolescent population).

Is anxiety a potential unmeasured variable in cognition-treatment outcome literature?

Research into the factors that predict treatment outcome, play an important role in generating hypotheses to inform future randomised clinical interventions and assess the effectiveness of current best-practice treatments (Byrd & Ho, 2011). Many factors have shown to increase the prevalence of relapse in SUD populations, such as psychological distress, socio-cultural demographics, treatment motivation and trait impulsivity (Brorson, et.al., 2013). Existing research, however, often neglects to include a wide range of treatment outcome relevant factors, often due to practical constraints, instead focusing solely on the variables directly related to their study hypotheses. In the current context, it may be that cognitive task performance and anxiety are related, and also that anxiety and outcome are related. As such, if anxiety is omitted from a study and only cognitive measures are included, these studies may overestimate the contribution of cognitive impairments as predictors of SUD and treatment outcomes. In the absence of a control, it is difficult to draw causal relationships between variables (Hill, 1965). While the present study controlled for some known covariates (e.g. general cognition, impulsivity, psychological distress), results were not as strong when compared to previous literature (Monterosso et. al., 2005, Stevens et.al., 2014, Field et.al., 2009). Studies such as Li et. al., (2009) and Monterosso et. al., (2005) controlled for premorbid intelligence and diagnosed comorbid mental disorders, however failed to control for other clinically significant state factors, such as current psychological distress. Previous significant results may therefore be influenced by unmeasured confounding variables and may overstate the true extent of shared variance between cognitive impairment and treatment outcomes. To support such a view, in an alcohol use population, when controlling for

other factors contributing to treatment outcomes (age, legal obligation, depressive symptoms and baseline alcohol use) anxiety sensitivity significantly was a significant predictor of early treatment dropout (Lejuez et.al., 2008).

There have been multiple studies among cannabis consumers demonstrating substantial correlations between anxiety sensitivity and extent of dependence and between anxiety sensitivity and treatment outcomes (Keough, Hendershot, Wardell, & Babdy, 2018; Zvolensky, et.al., 2018; Norberg, Olivier, Schmidt, & Zvolensky, 2014). Zvolesky et.al. (2018) found when controlling for all other factors tested (gender, years of cannabis use, negative affectivity, nicotine and alcohol use) anxiety sensitivity significantly explained variance in cannabis use problems (3%), perceived barriers to quitting (7%) and fear of quitting (11%). A study conducted by Keough et.al. (2018) found significant moderate correlations between impulsivity (negative urgency) and both anxiety sensitivity (r = .59, p <.01) and cannabis problems (r =.38, p <.01). Norberg, Olivier, Schmidt, & Zvolensky (2014) found evidence to suggest anxiety could be a mediating variable between between cannabis severity and early drop-out, with results showing a partial indirect effect. Similarly, a systematic review of a large number of correlates of treatment drop-out, identified medium to large effect sizes between early drop-out and anxiety (Brorson et. al., 2013). Given these shared relationships between cognition, anxiety and outcome, longitudinal rather than cross-sectional studies are needed to determine whether cognition or anxiety is the key driver of the relationship with outcome (Hill, 1965).

Limitations of study

Drug-based research does not have the ability to utilise a control/no treatment group or randomise conditions. Therefore, it is difficult to draw strong inferences about causality (Hill, 1965). Preexisting differences between participants may predispose them to particular patterns of drug use seen in the study. Research suggests SUD is often a self-medicating mechanism for individuals suffering depression and/or anxiety (Parks & Kennedy, 2004). Many participants scored high on psychological distress measures, which as previously discussed may have contributed to results of the study.

Self-selected groups also include inherent bias and therefore fails to provide a representation of the general SUD population (Curran, 2000). Participants in CTx showed a DSM-IV moderate to severe SUD symptom count. While inclusion criteria for Sativex trial, required participants to have previous unsuccessful treatment attempts. These samples are therefore representative of severe SUD and not the general drug using population. Sativex trial used data from the placebo group of a Randomised Control drug Trial (RCT). Meta-analysis shows RCT drop-out to be on average higher than the general clinical population (Kemmler, Hummer, and Widschwendter, 2005). On average general clinical drop out at 4 weeks is 55% (AIHW, 2017). While on average drop-out in placebo arm RCT is 60.2 % overall (Kemmler, Hummer, and Widschwendter, 2005). Results therefore may not be easily generalisable in a clinical setting Further research in the general clinical population with a wider spread of participants across levels of SUD severity would be ideal.

Results from self-reported measures of previous drug use are reliant on the honesty of participant and thus subject to individual bias. The present study used a TLFB to measure baseline drug use and both AUDADIS-5 (CTx) and CPQ (Sativex trial). Using this method however do fail to quantify the purity and content of illicit substances consumed. The TLFB collects data as to quantity of substance consumed but not how strong/pure the substance is. This may have added variance to results. The study also focused on the participant's main substance and did not account for potential poly-substance use. This may also have added variance to results found It is therefore expected that self-report measures of previous drug use and severity of dependence in this study are to be imprecise to some extent. However, Harrison, Martin, Enev and Harrington (2007) found agreement between hair and urine samples and self-report measures of previous drug use on a range of illicit substances to be 91.5%. These results were similar (between 71% and 95%) in a systematic review conducted by Darke (1998).

Studies have consistently found impairments in cognitive functioning across all drug type (Manning et. al., 2017). Sativex trial data consist of a cannabis use population. CTx sample consisted of a majority alcohol population. Greater generalisability in drug type would enhance future research. Difficultly in recruitment for the originally proposed study lead to a small sample size. Underpowered studies can yield false positive or null findings (Button et al., 2013). Results reported from CTx study are therefore more susceptible to type one and two errors. Sativex trail data however did met power calculations for reliable identification of a statistically significant effect.

Brorson et.al. (2013) identified mixed results in studies investigating the association between motivation and treatment drop out. Two studies found no significant relationship between motivation and dropping out, whereas one study reported a positive association. According to the transtheoretical model of stages of change, only 20% of those presenting for treatment are ready to take action and modify their behaviour, experiences, and/or environment to overcome their problems (Norcross, Krebs,& Porchaska, 2011). As the studies recruitment strategy was at arm's length and required self-selecting, the sample of participants may have been more intrinsically motivated at baseline to stay the course of treatment, therefore amplifying the significant results found for treatment readiness in this study. Despite the strength of this study in controlling for a number of potential covariates, the study was not able to measure all known factors contributing to treatment outcomes. This study assessed readiness to change and found significant associations between readiness and both cognitive mechanisms and dependence. The study however did not include other potential treatment factors such as treatment setting, duration, satisfaction or therapeutic alliance. Fewer studies have explored the relationships between these factors and treatment outcome (Brorson et.al., 2013).

Implications and directions for future research

There has been much research into individual factors contribute to treatment outcomes in out-patient talk-based therapy (Turner et.al., 2009; Stevens et.al., 2015), but lack an overarching theoretical framework. Engagement in treatment programs is necessary for successful rehabilitation, with a minimum of three months recommended (Katz, et. al. 2004). However, more than half (55%) of treatment seekers drop-out after less than a month (AIHW, 2017). Researchers argue that

cognitive deficits may interfere with treatment seekers ability to engage in or benefit from these treatments (Lyvers, 2000) with severity of SUD shown to increase in cases where treatment is unsuccessful or underutilized (Baconi et al., 2015). The study shows some evidence in support of the theoretical framework proposed by Manning et.al.(2017). In understanding the theoretical framework underpinning cognitive impairments and their relationship to treatment outcomes, interventions can be created to address these impairments and to help treatment seekers engage more effectively in treatment. This framework merits further critical investigation and expansion to consider a range of other factors contributing to outcome, and also the therapeutic processes that may be affected by cognitive problems.

The study findings also highlight anxiety as a possible unmeasured variable in previous cognition-outcome literature. There is much evidence for psychological distress as a strong predictor of treatment outcomes, however many previous studies fail to control for the variable when assessing associations between cognitive impairments and treatment outcomes. The main advantage of this study is its comprehensive covariate measures. To achieve better validity and re-test reliability when measuring previous ability of cognitive impairment, future studies should control for known factors of poor treatment outcomes (in particular anxiety and readiness to change). To build upon the current study, it would be interesting to explore the relationship between anxiety, cognitive impairments and treatment outcomes, as the study and previous literature indicate anxiety to be a possible mediatory variable .

Systematic review found traditional (12 steps program) approaches to therapy were found be less effective in comorbid anxiety and SUD populations when compared to pure SUD populations (Smith & Book, 2010). There are a number of interventions available for anxiety and anxiety sensitivity, for both top-down inhibitory control, and bottom-up drives. CBT was found most effective by Smith and Book (2010). Other common psychosocial therapies include MET and psychodynamic therapy/interpersonal therapy (Bandelow, Michaelis, & Wedkind, 2017). However, there is a lack of understating in how these interventions relate to outcomes in SUD populations. Therefore, it is difficult to assess which to use to support better clinical outcomes in treatment. As resources are limited, more research is needed in assessing outcomes of treatment in clinical populations, so that when evidence based clinical interventions are created, there is greater validity and thus therapeutic value.

Few studies have explored the relationships between DD and early-dropout rates, with much focus on DD as a predictor of relapse (Stevens el.al., 2014). Out-patient therapy is largely based around goal setting, thus, the ability to see and choose long term progress rather than the immediate gratification is necessary for therapy success. Correlations between top-down DD and dependence was significant treatment. However, limited time frame of study and low attrition rate at one-month follow provided insufficient data to measures treatment outcome in CTx. Further research exploring the relationship between DD and treatment outcomes would bridge the gap in previous literature.

Summary and Conclusions

In summary, the aim of the current study was to test the theoretical framework proposed by Manning et al (2017) that suggests that severity of dependence is associated with impairments in top-down inhibitory control and increases in bottom-up substance related drives, and that these cognitive measures are, in turn, related to treatment outcomes.

The study findings showed mixed evidence to support the theory underpinning the framework. Response inhibition (SST, top-down measure) and attentional bias (DP, bottom-up measure) were not significantly associated with severity of SUD. However, decision making (DD, top-down measure) and compulsivity (MCQ, bottom-up measure) to be significantly associated with severity of SUD in the two studies reported here.

The study findings did not support the predictions made by the framework. Greater bottom-up drives (MCQ compulsivity) and poorer top-down inhibitory control (SST) were not predictive of poorer treatment outcomes. Previous studies analyzing the relation between cognition and treatment outcomes failed to control for psychological distress and readiness to change. After controlling for other key correlates of treatment dropout (anxiety, and readiness to change), top-down (SST) measure was significantly associated with treatment outcomes.

In conclusion, the findings of the current study show some support for the theoretical framework proposed by Manning et al (2017). The findings highlight the multifaceted way in which people can remain stuck in substance use disorder, and requires further research attention in order to identify cognitive interventions that will be the most complementary to existing treatments.

References

Acosta, M. C., Marsch, L. A., Xie, H., Guarino, H., & Aponte-Melendez, Y. (2012). A web-based behavior therapy program influences the association between cognitive functioning and retention and abstinence in clients receiving methadone maintenance treatment. *Journal of dual diagnosis*, *8*(4), 283-293. doi: https://doi.org/10.1080/15504263.2012.723317

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Andrews, G., & Slade, T. (2001). Interpreting scores on the Kessler psychological distress scale (K10). *Australian and New Zealand journal of public health*, *25*(6), 494-497. doi: https://doi.org/10.1111/j.1467-842X.2001.tb00310.x.

Antony, M. M., Bieling, P. J., Cox, B. J., Enns, M. W., & Swinson, R. P. (1998). Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. *Psychological assessment*, *10*(2), 176. doi: 10027417230

Australian Institute of Health and Welfare (2017) *Alcohol and other drug treatment services in Australia 2016-17.* Retrieved from https://www.aihw.gov.au/getmedia/6ada5e0f-40ff-459b-ae6c-b45845a37ccc/aihw-hse-207.pdf.aspx?inline=true.

Ball, S. A., Carroll, K. M., Canning-Ball, M., & Rounsaville, B. J. (2006). Reasons for dropout from drug abuse treatment: Symptoms, personality, and

motivation. *Addictive behaviors*, *31*(2), 320-330. doi: https://doi.org/10.1016/j.addbeh.2005.05.013

Bandelow, B., Michaelis, S., & Wedekind, D. (2017). Treatment of anxiety disorders. *Dialogues in clinical neuroscience*, *19*(2), 93.

Bhardwaj, A. K., Allsop, D. J., J Copeland, J., McGregor, I. S., Dunlop, A., Shanahan, M., … & Lintzeris, N. (2018). Randomised Controlled Trial (RCT) of cannabinoid replacement therapy (Nabiximols) for the management of treatment-resistant cannabis dependent patients: a study protocol. *BMC Psychiatry, 18* (140). https://doi.org/10.1186/s12888-018-1682-2.

Boehler, C. N., Appelbaum, L. G., Krebs, R. M., Hopf, J. M., & Woldorff, M. G. (2012). The influence of different Stop-signal response time estimation procedures on behavior–behavior and brain–behavior correlations. *Behavioural brain research*, *229*(1), 123-130. doi: https://doi.org/10.1016/j.bbr.2012.01.003

Brorson, H. H., Arnevik, E. A., Rand-Hendriksen, K., & Duckert, F. (2013). Drop-out from addiction treatment: a systematic review of risk factors. *Clinical psychology review*, *33*(8), 1010-1024. doi : https://doi.org/10.1016/j.cpr.2013.07.007

Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*(5), 365.

Byrd, J. B., & Ho, P. M. (2011). The possibility of unmeasured confounding variables in observational studies: a forgotten fact?. doi: http://dx.doi.org/10.1136/heartjnl-2011-300630

Carpenter, K. M., Martinez, D., Vadhan, N. P., Barnes-Holmes, D., & Nunes, E. V. (2012). Measures of attentional bias and relational responding are associated with behavioral treatment outcome for cocaine dependence. *The American journal of drug and alcohol abuse*, *38*(2), 146-154. doi: https://doi.org/10.3109/00952990.2011.643986

Cardinal, R. N., Pennicott, D. R., Lakmali, C., Robbins, T. W., & Everitt, B. J. (2001). Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science*, *292*(5526), 2499-2501.

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. *Journal of personality and social psychology*, *67*(2), 319.

Cash, C., Peacock, A., Barrington, H., Sinnett, N., & Bruno, R. (2015). Detecting impairment: sensitive cognitive measures of dose-related acute alcohol intoxication. Journal of psychopharmacology, 29(4), 436-446. doi: https://doi.org/10.1177/0269881115570080

Christiansen, P., Mansfield, R., Duckworth, J., Field, M., & Jones, A. (2015). Internal reliability of the alcohol-related visual probe task is increased by utilising personalised stimuli and eye-tracking. *Drug and alcohol dependence*, *155*, 170-174. doi: https://doi.org/10.1016/j.drugalcdep.2015.07.672.

Christiansen, P., Schoenmakers, T. M., & Field, M. (2015). Less than meets the eye: Reappraising the clinical relevance of attentional bias in addiction. *Addictive behaviors*, *44*, 43-50. doi: https://doi.org/10.1016/j.addbeh.2014.10.005

Collins, D., & Lapsley, H. M. (2008). *The costs of tobacco, alcohol and illicit drug abuse to Australian society in 2004/05*(pp. 41-47). Canberra: Department of Health and Ageing.

Copeland, J., Gilmour, S., Gates, P., & Swift, W. (2005). The Cannabis Problems Questionnaire: factor structure, reliability, and validity. *Drug and Alcohol Dependence*, *80*(3), 313-319. doi: https://doi.org/10.1016/j.drugalcdep.2005.04.009

Copersino, M. L. (2017). Cognitive mechanisms and therapeutic targets of addiction. *Current opinion in behavioral sciences*, *13*, 91-98. doi: https://doi.org/10.1016/j.cobeha.2016.11.005

Cox WM, Hogan LM, Kristian MR, & Race JH (2002). Alcohol attentional bias as a predictor of alcohol abusers' treatment outcome. *Drug Alcohol Depend. 68,* 237–243. doi: https://doi.org/10.1016/S0376-8716(02)00219-3.

Department of Health (2004) 3.3 The stages-of-change model. *Module 9: Working with Young People on AOD Issues: Learner's Workbook.* Retrieved from http://www.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-pubs-front9-wk-toc~drugtreat-pubs-front9-wk-secb~drugtreat-pubs-front9-wk-secb-3~drugtreat-pubs-front9-wk-secb-3-3.

Duresso, S. W., Matthews, A. J., Ferguson, S. G., & Bruno, R. (2016). Is khat use disorder a valid diagnostic entity?. *Addiction*, *111*(9), 1666-1676. doi: 10.1111/add.13421.

Elman, I., & Borsook, D. (2016). Common brain mechanisms of chronic pain and addiction. *Neuron*, *89*(1), 11-36. doi: https://doi.org/10.1016/j.neuron.2015.11.027

Eysenck, S. B., Pearson, P. R., Easting, G., & Allsopp, J. F. (1985). Age norms for impulsiveness, venturesomeness and empathy in adults. *Personality and individual differences*, *6*(5), 613-619. doi: https://doi.org/10.1016/0191-8869(85)90011-X

Fernández-Serrano, M. J., Pérez-García, M., & Verdejo-García, A. (2011). What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance?. *Neuroscience & Biobehavioral Reviews*, *35*(3), 377-406. doi: https://doi.org/10.1016/j.neubiorev.2010.04.008

Fernandez-Serrano MJ, Perales JC, Moreno-Lopez L, Perez-Garcia M, & Verdejo-Garcia A (2012). Neuropsychological profiling of impulsivity and compulsivity in cocaine dependent individuals. *Psychopharmacology*, *219*, 673–683. doi: 10.1007/s00213-011-2485-z.

Field M, & Cox WM (2008). Attentional bias in addictive behaviors: A review of its development, causes, and consequences. *Drug and Alcohol Dependence*, *97*, 1–20. doi: https://doi.org/10.1016/j.drugalcdep.2008.03.030.

Field, M., Marhe, R., & Franken, I. H. (2014). The clinical relevance of attentional bias in substance use disorders. *CNS spectrums*, *19*(3), 225-230. doi: https://doi.org/10.1017/S1092852913000321

Field, M., Mogg, K., Zetteler, J., & Bradley, B. P. (2004). Attentional biases for alcohol cues in heavy and light social drinkers: the roles of initial orienting and maintained attention. *Psychopharmacology*, *176*(1), 88-93. doi: 10.1007/s00213-003-1689-2

Field, M., Munafò, M. R., & Franken, I. H. (2009). A meta-analytic investigation of the relationship between attentional bias and subjective craving in substance abuse. *Psychological bulletin*, *135*(4), 589.

Fillmore, M.T., Rush, C.R., 2002. Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend, 66:* 265–273.

Gates, P. J. (2017). Psychosocial interventions for cannabis use disorder. *Cochrane Database of Systematic Reviews*, (4). Retrieved from https://login.ezproxy.utas.edu.au/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edschh&AN=edschh.CD005336&site=eds-live

Green, R. E., Melo, B., Christensen, B., Ngo, L. A., Monette, G., & Bradbury, C. (2008). Measuring premorbid IQ in traumatic brain injury: an examination of the validity of the Wechsler Test of Adult Reading (WTAR). *Journal of Clinical and Experimental Neuropsychology*, *30*(2), 163-172. doi: https://doi.org/10.1080/13803390701300524.

Hagen, E., Erga, A. H., Hagen, K. P., Nesvag, S. M., McKay, J. R., Lundervold, A. J., Walderhaug, E. (2017). One-year sobriety improves satisfaction with life,

executive functions and psychological distress among patients with polysubstance use disorder. *Journal of Substance Abuse Treatment,* 76, 81-87. doi: https://doi.org/10.1016/j.jsat.2017.01.016

Hasin, D. S., Greenstein, E., Aivadyan, C., Stohl, M., Aharonovich, E., Saha, T., ... & Grant, B. F. (2015). The Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5): procedural validity of substance use disorders modules through clinical re-appraisal in a general population sample. *Drug and alcohol dependence*, *148*, 40-46. doi: https://doi.org/10.1016/j.drugalcdep.2014.12.011.

Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., ... & Schuckit, M. (2013). DSM-5 criteria for substance use disorders: recommendations and rationale. *American Journal of Psychiatry*, *170*(8), 834-851. doi: https://doi.org/10.1176/appi.ajp.2013.12060782.

Harrison, L. D., Martin, S. S., Enev, T., & Harrington, D. (2007). Comparing drug testing and self-report of drug use among youths and young adults in the general population. *Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies*.

Heishman, S. J., Singleton, E. G., & Liguori, A. (2001). Marijuana Craving Questionnaire: Development and initial validation of a self-report instrument. *Addiction*, *96*(7), 1023-1034. doi: https://doi.org/10.1046/j.1360-0443.2001.967102312.x.

Hjorthøj, C. R., Hjorthøj, A. R., & Nordentoft, M. (2012). Validity of timeline follow-back for self-reported use of cannabis and other illicit substances—

systematic review and meta-analysis. *Addictive behaviors*, *37*(3), 225-233. doi: https://doi.org/10.1016/j.addbeh.2011.11.025.

Katz, E.C., Brown, B.S., Schwartz, R.P., Weintraub, E., Barksdale, W., & Robinson, R. (2004) Role induction: A method for enhancing early retention in outpatient drug-free treatment. *Journal of Consulting and Clinical Psychology*. 72, 27–234

Kemmler, G., Hummer, M., Widschwendter, C., & Fleischhacker, W. W. (2005). Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis. *Archives of General Psychiatry*, *62*(12), 1305-1312. doi: 10.1001/archpsyc.62.12.1305

Keough, M. T., Penniston, T. L., Vilhena-Churchill, N., Bagby, R. M., & Quilty, L. C. (2018). Depression symptoms and reasons for gambling sequentially mediate the associations between insecure attachment styles and problem gambling. *Addictive behaviors*, *78*, 166-172. doi: https://doi.org/10.1016/j.addbeh.2017.11.018

Kessler, R. C., Andrews, G., Colpe, L. J., Hiripi, E., Mroczek, D. K., Normand, S. L., ... & Zaslavsky, A. M. (2002). Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychological medicine*, *32*(6), 959-976. doi: https://doi.org/10.1017/S0033291702006074.

Klimas, J., Field, C. A., Cullen, W., O'Gorman, C. S., Glynn, L. G., Keenan, E., ... & Dunne, C. (2012). Psychosocial interventions to reduce alcohol consumption

in concurrent problem alcohol and illicit drug users. *Cochrane Database of Systematic Reviews*, (11).

Kirby, K. N., Petry, N. M., & Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *Journal of Experimental psychology: general*, *128*(1), 78.

Lancaster, B.P. (1999). Defining and Interpreting Supresor Efects: Advantages and Limitations. *Southwest Educational Research Asociation*. doi: https://files.eric.ed.gov/fulltext/ED426097.pdf

Le Berre, A. P., Vabret, F., Cauvin, C., Pinon, K., Allain, P., Pitel, A. L., ... & Beaunieux, H. (2012). Cognitive barriers to readiness to change in alcohol-dependent patients. *Alcoholism: Clinical and Experimental Research*, *36*(9), 1542-1549. doi: https://doi.org/10.1111/j.1530-0277.2012.01760.x

Leeman, R. F., Robinson, C. D., Waters, A. J., & Sofuoglu, M. (2014). A critical review of the literature on attentional bias in cocaine use disorder and suggestions for future research. *Experimental and clinical psychopharmacology*, *22*(6), 469.

Li, C.-s. R., Luo, X., Yan, P., Bergquist, K., Sinha, R., & Akine, A.,(2009). Altered impulse control in alcohol independence: Neural measures of stop signal performance. *Alcoholism: Clinical and Experimental Research, 33*(4), 740-750.

Loveland, D., & Driscoll, H. (2014). Examining attrition rates at one specialty addiction treatment provider in the United States: a case study using a

retrospective chart review. *Substance abuse treatment, prevention, and policy*, *9*(1), 41. doi: https://doi.org/10.1186/1747-597X-9-41

Lyvers, M. (2000). " Loss of control" in alcoholism and drug addiction: a neuroscientific interpretation. *Experimental and clinical psychopharmacology*, *8*(2), 225. doi: http://dx.doi.org/10.1037/1064-1297.8.2.225

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour research and therapy*, *33*(3), 335-343. doi: https://doi.org/10.1016/0005-7967(94)00075-U.

Lubman, D. (2015). Treatment of Comorbid Depression and Substance Abuse in YoungPeople. *ClinicalTrials.gov*, EBSCO*host* (accessed May 6, 2018).

Lubman, D. I., Peters, L. A., Mogg, K., Bradley, B. P., & Deakin, J. F. W. (2000). Attentional bias for drug cues in opiate dependence. *Psychological medicine*, *30*(1), 169-175.

Lubman, D. I., Yücel, M., & Pantelis, C. (2004). Addiction, a condition of compulsive behaviour? Neuroimaging and neuropsychological evidence of inhibitory dysregulation. *Addiction*, *99*(12), 1491-1502. doi: https://doi.org/10.1111/j.1360-0443.2004.00808.x

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., & Munafò, M. R. (2011). Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology*, *216*(3), 305-321. doi: 10.1007/s00213-011-2229-0.

Manning, V., Verdejo-Garcia, A., & Lubman, D. I. (2017). Neurocognitive impairment in addiction and opportunities for intervention. *Current Opinion in Behavioral Sciences, 13*, 40-45. doi: https://doi.org/10.1016/j.cobeha.2016.10.003.

Marceau, E. M., Lunn, J., Berry, J., Kelly, P. J., & Solowij, N. (2016). The Montreal Cognitive Assessment (MoCA) is sensitive to head injury and cognitive impairment in a residential alcohol and other drug therapeutic community. *Journal of substance abuse treatment*, *66*, 30-36. doi: https://doi.org/10.1016/j.jsat.2016.03.002.

Mazur, J. E. (1987). An adjusting procedure for studying delayed reinforcement. In: Commons, M.L., Mazur, J.E., Nevin, J.A., Rachlin, H. (Eds.), *Quantitative analysis of behavior: vol 5. The effect of delay and intervening events on reinforcement value.* (pp 55–73). Hillsdale; Erlbaum Press (1987).

Miller, M. A., & Fillmore, M. T. (2010). The effect of image complexity on attentional bias towards alcohol-related images in adult drinkers. *Addiction*, *105*(5), 883-890. doi: https://doi.org/10.1111/j.1360-0443.2009.02860.x.

Miller, W. R., & Tonigan, J. S. (1996). Assessing drinkers' motivation for change: the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES). *Psychology of addictive behaviors*, *10*(2), 81.

Mitchell, D., & Angelone, D. J. (2006). Assessing the validity of the Stages of Change Readiness and Treatment Eagerness Scale with treatment-seeking

military service members. *Military medicine*, *171*(9), 900-904. doi: https://doi.org/10.7205/MILMED.171.9.900.

National Institute on Drug Abuse (2009). *Principles of Drug Addiction Treatment: A Research-Based Guide*. Retrieved from https://www.drugabuse.gov/sites/default/files/podat_1.pdf.

Norberg, M. M., Olivier, J., Schmidt, N. B., & Zvolensky, M. J. (2014). Cannabis Use among Treatment-Seeking Smokers: Motives and the Moderating Effects of Anxiety Sensitivity. *The American journal on addictions*, *23*(1), 7-14. doi: https://doi.org/10.1111/j.1521-0391.2013.12054.x

Norcross, J. C., Krebs, P. M., & Prochaska, J. O. (2011). Stages of change. *Journal of clinical psychology*, *67*(2), 143-154. doi: https://doi.org/10.1002/jclp.20758

Nuijten, M., Blanken, P., Van den Brink, W., Goudriaan, A. E., & Hendriks, V. M. (2016). Impulsivity and attentional bias as predictors of modafinil treatment outcome for retention and drug use in crack-cocaine dependent patients: Results of a randomised controlled trial. *Journal of Psychopharmacology*, *30*(7), 616-626. doi: https://doi.org/10.1177/0269881116645268

Palmer, R. S., Murphy, M. K., Piselli, A. and Ball, S. A. 2009. Substance user treatment drop-out from client and clinician perspectives: A pilot study. *Substance Use & Misuse*, 44: 1021–1038.

Parks, K. A., & Kennedy, C. L. (2004). Club drugs: reasons for and consequences of use. *Journal of psychoactive drugs*, *36*(3), 295-302. doi: https://doi.org/10.1080/02791072.2004.10400030

Pencer, A. & Addington, J. (2003) Substance use and cognition in early psychosis. *J Psychiatry Neurosci*. *28*(1):48-54.

Pérez-Mañá, C. (2013). Efficacy of psychostimulant drugs for amphetamine abuse or dependence. *Cochrane Database of Systematic Reviews*, (9). Retrieved from https://login.ezproxy.utas.edu.au/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edschh&AN=edschh.CD009695&site=eds-live

Peters, E. N., Petry, N. M., LaPaglia, D. M., Reynolds, B., & Carroll, K. M. (2013). Delay discounting in adults receiving treatment for marijuana dependence. *Experimental and clinical psychopharmacology*, *21*(1), 46. doi: 10.1037/a0030943

Robinson, T. E., & Berridge, K. C. (2000). The psychology and neurobiology of addiction: an incentive–sensitization view. *Addiction*, *95*(8s2), 91-117. doi: https://doi.org/10.1046/j.1360-0443.95.8s2.19.x

Rooke, S. E., Hine, D. W., & Thorsteinsson, E. B. (2008). Implicit cognition and substance use: A meta-analysis. *Addictive behaviors*, *33*(10), 1314-1328. doi : https://doi.org/10.1016/j.addbeh.2008.06.009

Rupp, C. I., Beck, J. K., Heinz, A., Kemmler, G., Manz, S., Tempel, K., . . . Bari, B. B. B. B. B. B.-J. B. B. C. C. C. C. D. W. D. F. F. F. G. G. H. H. H. H. J. J. J. K. L. (2016). Impulsivity and alcohol dependence treatment completion: Is

there a neurocognitive risk factor at treatment entry? Alcoholism: Clinical and Experimental Research, 40(1), 152-160.

Russo, P. M., Leone, L., & De Pascalis, V. (2011). Cross-cultural validity of the I7 impulsiveness-venturesomeness-empathy scales: evidence from the Italian I7. *Comprehensive psychiatry*, *52*(4), 446-452. doi: https://doi.org/10.1016/j.comppsych.2010.07.008.

Şimşek, M., Dinç, M., & Ögel, K. (2018). Determinants of the addiction treatment drop-out rates in an addiction counseling centre: a cross-sectional study. *Psychiatry and Clinical Psychopharmacology*, 1-9. doi: https://doi.org/10.1080/24750573.2018.1505283

Smith, J. L., Mattick, R. P., Jamadar, S. D., & Iredale, J. M. (2014). Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. Drug and alcohol dependence, 145, 1-33. doi: https://doi.org/10.1016/j.drugalcdep.2014.08.009

Stevens, L., Goudriaan, A. E., Verdejo-Garcia, A., Dom, G., Roeyers, H., & Vanderplasschen, W. (2015). Impulsive choice predicts short-term relapse in substance-dependent individuals attending an in-patient detoxification programme. *Psychological medicine*, *45*(10), 2083-2093. doi: https://doi.org/10.1017/S003329171500001X

Stevens, L., Verdejo-García, A., Roeyers, H., Goudriaan, A. E., & Vanderplasschen, W. (2015). Delay discounting, treatment motivation and treatment retention among substance-dependent individuals attending an in inpatient

detoxification program. *Journal of substance abuse treatment*, *49*, 58-64. doi: https://doi.org/10.1016/j.jsat.2014.08.007

Sobell, L. C., & Sobell, M. B. (1992). Timeline follow-back. In *Measuring alcohol consumption* (pp. 41-72). Humana Press, Totowa, NJ.

Sofuoglu, M, DeVito, E, Waters, A, & Carroll, K. (2013). Cognitive enhancement as a treatment for drug addictions. *Neuropharmacology, 64:*452-463. doi: 10.1016/j.neuropharm.2012.06.021.

Stanger, C., Ryan, S. R., Fu, H., Landes, R. D., Jones, B. A., Bickel, W. K., & Budney, A. J. (2012). Delay discounting predicts adolescent substance abuse treatment outcome. *Experimental and clinical psychopharmacology*, *20*(3), 205. doi: 10.1037/a0026543.

Substance Abuse and Mental Health Services Administration (2016) *National Survey on Drug Use and Health*. Retrieved from https://www.samhsa.gov/data/sites/default/files/...2016/NSDUH-DetTabs-2016.pdf

Townshend, J., & Duka, T. (2001). Attentional bias associated with alcohol cues: differences between heavy and occasional social drinkers. *Psychopharmacology*, *157*(1), 67-74. doi: https://doi.org/10.1007/s002130100764

Turner, T. H., LaRowe, S., Horner, M. D., Herron, J., & Malcolm, R. (2009). Measures of cognitive functioning as predictors of treatment outcome for cocaine dependence. *Journal of substance abuse treatment*, *37*(4), 328-334. doi: https://doi.org/10.1016/j.jsat.2009.03.009

United Nations Office on Drugs and Crime (2017) *World Drug Report 2016.* Retrieved from https://www.unodc.org/wdr2017/index.html.

Volkow, N. D., Fowler, J. S., & Wang, G. J. (2003). The addicted human brain: insights from imaging studies. *The Journal of clinical investigation*, *111*(10), 1444-1451.

Volkow, N. D., & Li, T. K. (2004). Drug addiction: the neurobiology of behaviour gone awry. *Nature Reviews Neuroscience*, *5*(12), 963.

Wileyto, E. P., Audrain-McGovern, J., Epstein, L. H. & Lerman, C. (2004). Using logistic regression to estimate delayed-discounting functions. *Behavior Research Methods, Instruments, & Computers, 36*(1), 41-51.

Winters, K. C., Fawkes, T., Fahnhorst, T., Botzet, A., & August, G. (2007). A synthesis review of exemplary drug abuse prevention programs in the United States. *Journal of Substance Abuse Treatment*, *32*(4), 371-380. doi: https://doi.org/10.1016/j.jsat.2006.10.002.

Yi, R., Mitchell, S. H., & Bickel, W. K. (2010). Delay discounting and substance abuse-dependence. *Impulsivity: The behavioral and neurological science of discounting*, 191-211. doi: http://dx.doi.org/10.1037/12069-007

Zilverstand, A., Parvaz, M. A., Moeller, S. J., & Goldstein, R. Z. (2016). Cognitive interventions for addiction medicine: understanding the underlying neurobiological mechanisms. In *Progress in brain research*. 224, pp. 285-304). doi: https://doi.org/10.1016/bs.pbr.2015.07.019

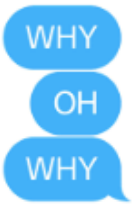
Zvolensky, M. J., Rogers, A. H., Manning, K., Hogan, J. B., Paulus, D. J., Buckner, J. D., ... & Schmidt, N. B. (2018). Anxiety sensitivity and cannabis use problems, perceived barriers for quitting, and fear of quitting. *Psychiatry research*, *263*, 115-120. doi: https://doi.org/10.1016/j.psychres.2018.03.006

Worley, M. J., Trim, R. S., Roesch, S. C., Mrnak-Meyer, J., Tate, S. R., & Brown, S. A. (2012). Comorbid depression and substance use disorder: Longitudinal associations between symptoms in a controlled trial. *Journal of substance abuse treatment*, *43*(3), 291-302. doi : https://doi.org/10.1016/j.jsat.2011.12.010.

Appendix

A. Recruitment Poster

Have you just started treatment for problems with alcohol or drug use? We need your brainpower!



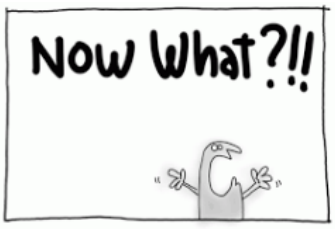
University researchers are studying how your thinking (memory, reaction time, decision making) relates to progress in treatment.

This will help us work out the types of thinking skills that are most closely related to good treatment outcomes. It will also help select 'brain training' packages that might help people get better results from treatment for their substance use.

If you're interested, there's a 60-90 minute session at the University, where you will complete some surveys and measures of your thinking. We'll provide you $40 for your time and expenses.

We'd also like to check in with you a month later to see how you're doing.

Three months later, we'd like to get you back to the university to do these measures again (we'll provide another $40 for this bit). With your approval we'd also like to ask your counsellor about your improvement over treatment.



Contact us on: ctxstudy@gmail.com

0434355925 OR http://goo.gl/FzZgUf

0434355925	ctxstudy@gmail.com	0434355925	ctxstudy@gmail.com	0434355925	ctxstudy@gmail.com	0434355925	ctxstudy@gmail.com	0434355925	ctxstudy@gmail.com	0434355925	ctxstudy@gmail.com	0434355925	ctxstudy@gmail.com	0434355925	ctxstudy@gmail.com	0434355925	ctxstudy@gmail.com	0434355925	ctxstudy@gmail.com

Appendix

B. Participant Information Sheet

Cognition and Drug Treatment Outcomes

Invitation

This is an independent study conducted by Associate Professor Raimondo Bruno, in the School of Medicine (Psychology) at the University of Tasmania.

What is the purpose of this study?

We are seeking to better understand how your thinking relates to progress in treatment for problems with substance use.

By 'thinking' we mean a range of different things, such as concentration, memory, attention, the ability to put the breaks on your responses, and your decision making about short and long term consequences. There has been a number of studies that have shown that these sorts of skills are related to how well people do in their chosen 'talk based' treatment for substance use problems (like counselling). There is also a number of training programs that are in development to help people improve on these aspects of thinking.

What we're aiming to do is to work out which are the best types of thinking skills to measure that are most closely associated with how well people go in treatment. We can then target these with particular brain training programs to see if they will help improve outcomes for people seeking treatment for problems with substance use.

Why have I been invited to participate?

We're inviting anyone who has just started treatment in 'talk-based' therapies (like counselling and psychology) for a problem with any substance they use (except for tobacco).

We don't want to get in the way of your treatment, though. It is important that you know that this study is completely independent from whatever service you are attending. We have invited people at all drug treatment services in Hobart to take part in this study. If you don't want to take part in this study, that is OK, and it is not going to have any impact on the way you are treated by this service. If you start taking part in this study, and decide that you don't want to continue, that's not going to have any impact on how your treatment service will treat you either.

What will I be asked to do?

There are a number of parts to this study.

After making sure that you are eligible to take part, there is a 60-90 minute research session at the University of Tasmania. Here we would ask you questions about your substance use, such as how often you have used in the last 4 weeks, and any problems you have been experiencing from the substance. You'll be asked about any feelings of craving for the substance you have problems with. There are also some questions about where you're at in terms of wanting to change your substance use. These will likely cover similar types of questions that your counsellor or psychologist asked in your first assessment session. There will be some questions about your mood and your personality style. For all of these, it is really important to know that if you're not comfortable about talking about these things, it's OK just to tell us that you don't want to talk about it, or to say you don't want to answer a particular question. We won't give you a hard time about it, and whatever you decide to do isn't going to impact on the way that your drug treatment provider treats you.

In this same session, there are a bundle of thinking tasks. These might ask you to pronounce some unusual words out loud (like 'yacht'), to pick the direction of an arrow on screen as quickly as possible, or say the colour that words are written in. There's also some tasks where you have to remember to hold back hitting a key on a keyboard every now and then after you have been responding as quickly as you can to targets on the screen. There's some tests of memory where you have to remember a number that has been shown to you. Lastly, there are some tests of the way you make decisions. One uses a virtual bunch of decks of cards which give you different monetary outcomes and you'll need to pick from each deck to try to get the best outcome at the end. The other asks you to make hypothetical decisions between whether you would prefer to have a small amount of money now or a larger amount of money later, over different amounts and timeframes.

This sounds like a lot but each of these things only takes 2-5 minutes, and you can take regular breaks (we'll remind you about this option).

The other bits of the study are:

- We'd like to ask if it is ok to check in with you by phone or email four weeks after you start treatment to see how you are going
- We'd like to ask if it is OK to check with your therapist / counsellor 12 weeks after you start treatment to see how many sessions you attend, and their opinion of your improvement over that time
- We'd like to invite you to come back to the University to repeat most of the things you did in that first research session, and also ask your opinion of your improvement over time.

It is important to know that it's up to you whether you want to do any of these bits of the study, and if you are only ok with some bits and not others, that's ok, you can still take part in the bits of the study that you are comfortable with.

Are there any possible benefits from participation in this study?

The main benefit from taking part in this study is making a contribution to helping understand how to improve outcomes for drug treatment.

We appreciate your time and inconvenience in contributing to research, and we are able to provide reimbursement of $40 for each of the sessions at the university ($80 in total).

Are there any possible risks from participation in this study?

There are a number of risks involved in taking part in this study, but they are quite similar to the risks involved in seeking treatment for your problem substance use.

Firstly, there are some questions about your mood. These might cause you to think about how your mental health is. If they cause you distress, this might be something you can discuss with your current counsellor / therapist. Or, if you need to discuss something straight away, there are a number of options available 24 hours a day, 7 days a week, including Lifeline (13 11 14), beyond blue (1300 22 4636) or counselling online (https://www.counsellingonline.org.au/)

Secondly, we are acutely aware of the degree of unfortunate social stigma that is associated with substance use. We have a number of steps in place to protect your confidentiality (more on this below). The other aspect of this is that there are legal issues associated with drug use. In this study, we have a number of questions that ask about your use of substances, and in some cases this may include illegal substances.

We will generally not disclose to anyone information about your use of substances without your consent. However, there may be some circumstances where we have to do so for legal reasons. In that case, the information could potentially be used against you in legal proceedings or otherwise (for example, information about drug use could be considered relevant in a criminal investigation or in relation to the Family Court). To our knowledge, researchers in this institution have not been required by law to provide information. Certainly, the investigators in this study have conducted interviews about substance use for the past 15 years with more than 3000 people and have never been required to provide any information. If, however, we were ever required to do so, we would do our best to notify you before disclosing it.

We have a number of protections in place to reduce this risk. Firstly, the consent forms with identifying information (such as your contact details) are kept separately from all other information from this study (such as the questions about your substance use). They are stored securely at the University. All information from the

study is stored only with a study ID (e.g. CTX777). As soon as you complete the study, any link between your identifying information and study ID is securely destroyed, making it very difficult for an individual person to be identified by their data.

What if I change my mind during or after the study?

As noted above, it is completely fine for you to decide not to answer any questions that you're not comfortable with. That won't affect your relationship with the university and it won't affect your treatment by your counsellor. The same applies if you start the study and then decide that it is not for you. You don't need to explain why.

If you decide that you don't want to be part of the study, and you let us know before the end of your participation in the study, we'll be able to work out which data is yours and we can delete all records and securely destroy any consent forms. If you let us know after you have finished all the parts of the study, we won't be able to remove your data because we would have destroyed the links between your identifying information and the study ID.

What will happen to the information when this study is over?

Identifying information will be destroyed as soon as any individual participant completes their part of the study. All the information about performance on the different tasks and the like are stored only using study ID. This will be stored in an electronic database, on secured University of Tasmania servers, and password protected. Hard copies (of your consent form using a pseudonym that doesn't link with a study ID) are stored in locked filing cabinets in University of Tasmania storage archives. Both electronic and hard copy data will be destroyed five years after the first publication from this study.

A reminder: any information obtained for the purpose of this study that can identify you will be destroyed as soon as you have completed your part in the study or withdrawn your consent. All information, regardless of whether it is identifying or not, will be treated as confidential and always securely stored. It would only be disclosed with your permission or in compliance with the law.

How will the results of the study be published?

Study findings will be presented in formal publications and in conference presentations to people in the substance use field. Only group level analyses will be reported, so there is no way that a particular individual could be identified in any publication. The results will be available on the university of Tasmania publications repository, WARP (https://rmdb.research.utas.edu.au/public/rmdb/q/warp_home) or specifically here: https://rmdb.research.utas.edu.au/public/rmdb/q/indiv_detail_warp_trans/3812#research-tab-5. You can also contact Raimondo Bruno directly here: Raimondo.Bruno@utas.edu.au

What if I have questions about this study?

If you have questions about the study, you can contact Raimondo Bruno at 03 6226 2240 or Raimondo.Bruno@utas.edu.au.

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study, please contact the Executive Officer of the HREC (Tasmania) Network on +61 3 6226 6254 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote ethics reference number H0017170.

Thank you for your interest in the study, and your time in reading this information sheet. This is for you to keep. If you want to take part in this study, there are three consent forms for you to complete. These will be stored separately from study documents.

Appendix

C. Ethics Approval Letter

Dear AssocProf Bruno,

Reference number: H0017170

Title: COGNITION AND DRUG TREATMENT OUTCOMES A PILOT STUDY

We are pleased to advise that this study has been approved by the Tasmanian Human Research Ethics Committee and a signed approval letter will be emailed to you provided we have received the signed copy of the final approved application. If you have not already done so, please submit your signed application to human.ethics@utas.edu.au.

Please be advised that the Chief Investigator cannot also sign in place of the Head of School/Department. Please note that if the Head of School/Department is listed as one of the investigators, this statement must be signed by an appropriate person, such as the Dean.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

In accordance with the National Statement on Ethical Conduct in Human Research, it is the responsibility of institutions and researchers to be aware of both general and specific legal requirements, wherever relevant. If researchers are uncertain they should seek legal advice to confirm that their proposed research is in compliant with the relevant laws. University of Tasmania researchers may seek legal advice from Legal Services at the University."

Please contact us if you require further information.

With kind regards

Heather Vail

Executive Officer | Health and Medical Human Research Ethics Committee

Research Integrity and Ethics Unit | Research Division

University of Tasmania

Heather.vail@utas.edu.au

+61 3 6226 5520

Appendix

D. Cognition and Drug Treatment Outcomes: Screening

What is this study about?

We are seeking to better understand how your thinking relates to progress in treatment for problems with substance use.

By 'thinking' we mean a range of different things, such as concentration, memory, attention, the ability to put the breaks on your responses, and your decision making about short and long term consequences. There has been a number of studies that have shown that these sorts of skills are related to how well people do in their chosen 'talk based' treatment for substance use problems (like counselling). There is also a number of training programs that are in development to help people improve on these aspects of thinking.

What we're aiming to do is to work out which are the best types of thinking skills to measure that are most closely associated with how well people go in treatment. We can then target these with particular brain training programs to see if they will help improve outcomes for people seeking treatment for problems with substance use.

Who are we inviting to participate?

We're inviting anyone who has just started treatment in 'talk-based' therapies (like counselling and psychology) for a problem with any substance they use (except for tobacco).

What does taking part involve?

After making sure that you are eligible to take part, there is a 60-90 minute research session at the University of Tasmania. In this session, we ask about your substance use, your treatment, and ask you to complete a bundle of thinking tasks. One month later, we'd like to give you a call to check in to see how you are going with your treatment. Three months later we'd like to invite you back to complete most of the things you did in the first session, to see how things have changed. You will be reimbursed $40 for each session you attend.

For more details about the study and what it involves, please click here. If you have any further questions about the study, email us at ctxstudy@gmail.com.

Are you over 18 years of age ?

- o Yes
- o No

What is your age in years? _____

What is your sex?

- Female
- Male
- Other

What is your main language ?

- English
- Other

What is your main language? _____

Have you started treatment (counselling, psychology, any 'talk therapy') for a problem with substance?

- Yes
- No

When did (or will) you start this treatment ? (please specify date - an estimate is fine) _____

What is the name of the service that you are attending for treatment? _____

How many sessions does your treatment provider offer per week? (leave blank if you don't know) _____

How many sessions have you attended so far? _____

Have you engaged in treatment before?

- Yes
- No

Has your treatment been required (mandated) by the court?

- Yes
- No

What is the main substance you are concerned about?

alcohol cannabis methamphetamine opioids other

Specify the other drug type _____

Are you taking medications for your substance use problem ?

- Yes
- No

What is the name of the medication?

_____

Are you currently in inpatient (hospitalised) withdrawal?

- Yes
- No

Are you in residential treatment program for your substance use problem? (e.g. admitted to a private hospital or a rehabilitation service?)

- Yes
- No

Thank you for answering the screening questionnaire, we appreciate your assistance. If you are eligible to participate, the researchers will be in contact with you as quickly as possible. All of your contact details will be kept confidential and are securely stored. You can use a fake name if you prefer!

Please email us at ctxstudy@gmail.com if you have any queries.

What is your e-mail address? This is so we can contact you.

_____

What is the phone number you are most easily reached on?

_____

Please indicate which days would best suit for us to come to the University for an 60-90 minute interview (if you are eligible)

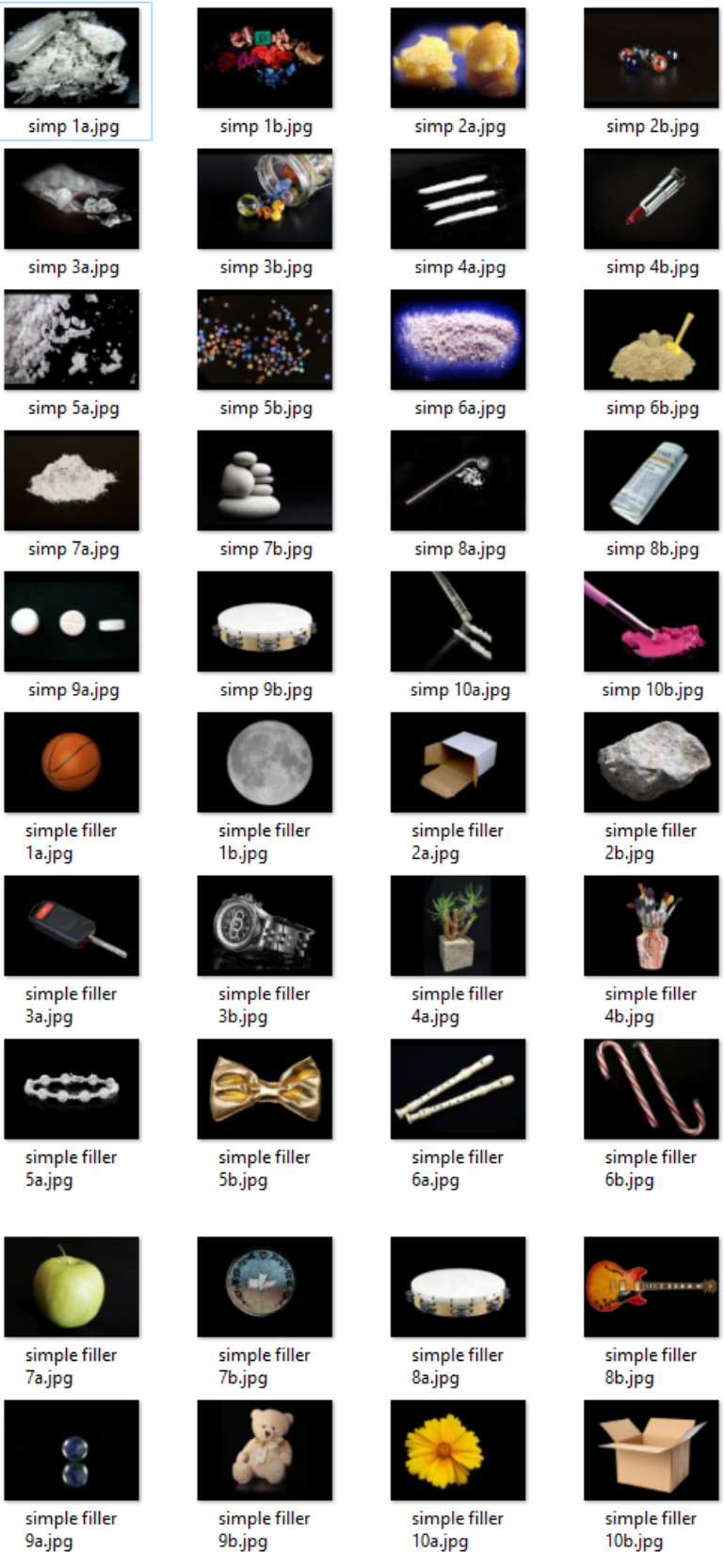
- Monday
- Tuesday
- Wednesday
- Thursday
- Friday
- Specify time
- 9am-12pm
- 12pm-3pm
- 3pm-6pm

Appendix

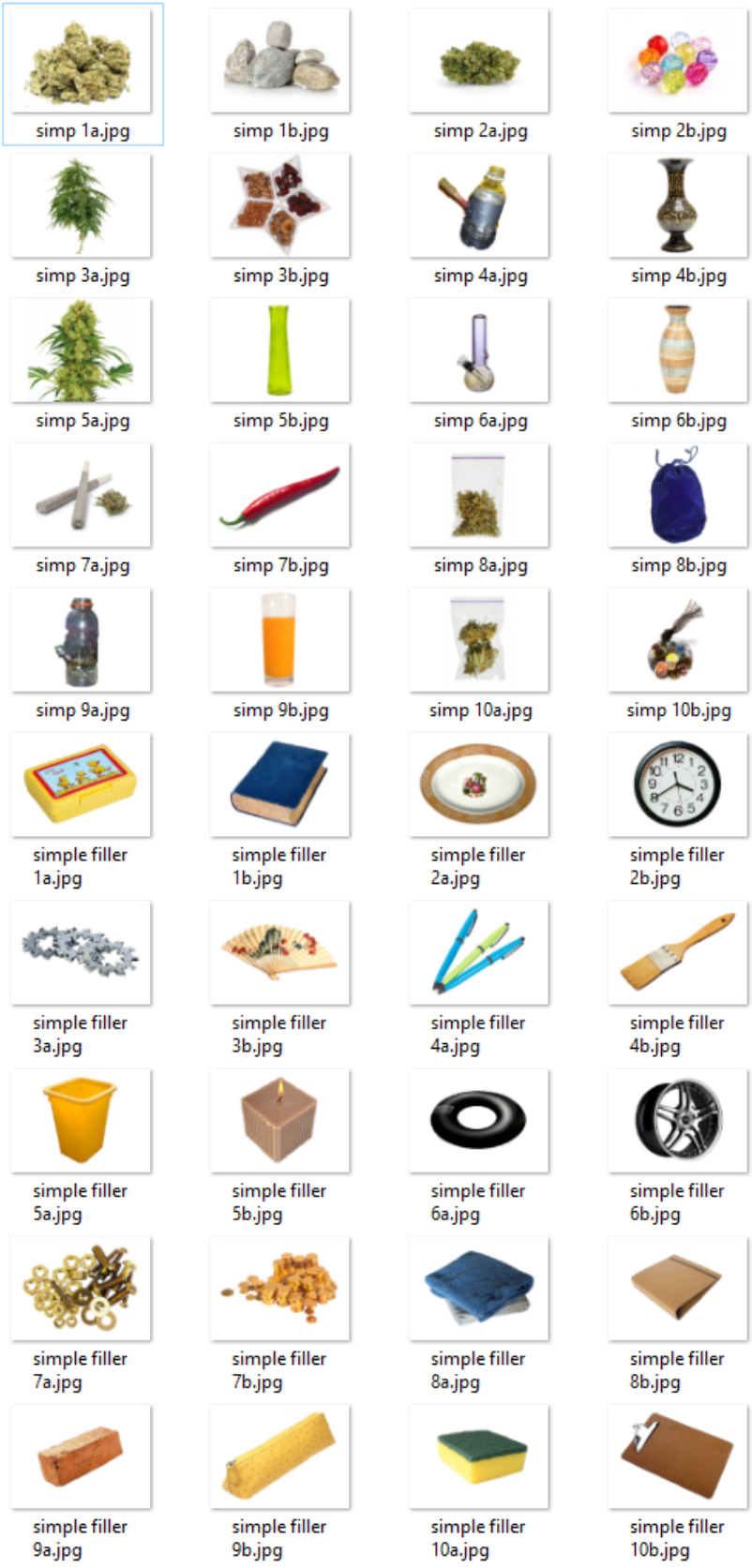
E. Attentional Bias Dot Probe Stimuli

Alcohol stimuli (*a stimuli) and matches (*b stimuli) and filler stimuli

Amphetamine stimuli (*a stimuli) and matches (*b stimuli) and filler stimuli



Cannabis stimuli (*a stimuli) and matches (*b stimuli) and filler stimuli



Opioid stimuli (*a stimuli) and matches (*b stimuli) and filler stimuli

Appendix

E. Experiment 1 CTx Data

Table 1 Correlations all variables measured in Experiment 1 CTx for both original data and data with outliers removed

Variables		DDRTms		SSRTms		DDlog *k*		Dependence		WTAR		MoCa		*k*10		Recognition		Ambivalence		Taking Steps		I7	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Bottom-Up (DPRTms)	o	-	-	.575	.177	.118	.801	-.096	.839	-.060	.911	.377	.461	-.289	.579	-.376	.462	-.466	.388	-.358	.486	.454	.366
	d	-	-	.755	.177	-.246	.638	-.096	.838	-.060	.911	.377	.461	-.289	.579	-.376	.462	-.436	.388	-.358	.486	.454	.366
Top-Down (SSRTms)	o			-	-	.406	.366	.287	.532	.312	.547	.664	.150	-.303	.560	-.263	.614	-.047	.930	.050	.926	-.198	.707
	d			-	-	-.044	.934	.287	.532	.312	.547	.664	.150	-.303	.560	-.263	.614	-.047	.930	.050	.926	-.198	.707
Top-Down (DD log *k*)	o					-	-	.516	.236	-.350	.496	.307	.554	.560	.361	.376	.462	.169	.748	-210	.689	.205	.697
	d					-	-	.813	.049*	-.729	.160	-.614	.271	.844	.072	.807	.099	.900	.037*	.668	.218	.135	.829
Dependence (DSM symptom count)	o							-	-	-.653	.161	-.497	.316	.842	.036*	.893	.017*	.746	.088	.410	.420	.107	.840
	d							-	-	-.653	.160	-.497	.316	.842	.036*	.893*	.017*	.746	.088	.410	.420	.107	.840
WTAR	o									-	-	.651	.161	.806	.53	-645	.167	-.352	.494	-.008	.998	-.748	.087
	d									-	-	.651	.161	-.806	.053	-.645	.167	-.352	.494	-.008	.988	-.748	.087
MoCa	o											-	-	-.622	.187	-.692	.128	-.452	.368	-.284	.585	-.282	.588

	d			-	-	-.622	.187	-.692	.128	-.452	.368	-.282	.585	-.282	.588
k10	o					-	-	.942	.005**	.532	.225	.124	.814	.322	.533
	d					-	-	.942	.005**	.582	.225	.124	.814	.322	.588
SOCRATES recognition	o							-	-	.712	112	.321	.535	.062	.907
	d							-	-	.712	.112	.321	.535	.062	.907
SOCRATES ambivalence	o									-	-	.872	.024*	-.337	.513
	d											.872	.024*	-.337	.513
SOCRATES taking steps	o											-	-	-.541	.268
	d													.541	.268
Impulsivity (I7)	o													-	-
	d													-	-

Note: o= original data, d= data without delayed discounting outliers, * $p < .05$, ** $p < .01$

Appendix

F. Experiment 2 Data

Table 1 Correlations all variables measured in Experiment 2 for both original data and data with participant with low SSRT scores removed

Variables		1		2		3		4		5		6		7		8		9		10	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
1.Bottom-Up (Compulsivity)	o	-	-	-.200	.110	.314	.010**	.115	.353	-.043	.733	.311	.010*	.178	.150	.358	.003**	-.125	.312	.071	.570
	s	-	-	-.217	.078	.314	.010**	.115	.353	-.043	.733	.311	.010*	.178	.150	.358**	.003	-.125	.312	.071	.570
2. Top-Down (SSRTms)	o			-	-	-.188	.134	-.066	.600	.157	.218	-.319	.010**	-.216	.084	-.265	.033	-.153	.224	-.105	.405
	s	-.217	.078	-	-	-.186	.133	-.074	.554	.115	.360	-.327	.007**	-.198	.109	-.281	.021*	-.140	.259	-.076	.541
3. Dependence	o					-	-	.014	.910	.017	.896	.556	<.001***	.662	<.001***	.473	<.001***	-.094	.450	-.028	.823
	s					-	-	.014	.910	.017	.896	.556	<.001***	.662	<.001**	.473	<.001***	-.094	.450	-.028	.823
4.Baseline Substance use	o	.115	.353	-.074	.554	.014	.910	-	-	-.196	.117	.040	.746	.002	.987	.088	.479	-.221	.073	-.152	.218
	s	.115	.358	-.074	.554	.014	.910	-	-	-.196	.117	.040	.746	.002	.987	.088	.479	-.221	.073	-.152	.218
5.WTAR	o									-	-	.023	.854	-.105	.405	.167	.185	-.200	.109	.048	.707
	s									-	-	.023	.854	-.105	.405	.167	.185	-.200	.109	.048	.707

6. Anxiety	o						-	-	.581	<.001**	.443	<.001**	-.078	.528	-.114	.356
	s						-	-	.581	<.001**	.443	<.001**	-.078	.528	-.114	.356
7. Depression	o	.662	<.001***	-.105	.405	.581	<.001***	-	-	.334	.006**	-.024	.847	.007	.953
	s	.662	<.001***	-.105	.405	.581	<.001***	-	-	.334	.006**	-.024	.847	.007	.953
8. Readiness to change	o					.443	<.001***			-	-	-.200	.104	-.081	.514
	s					.443	<.001***			-	-	-.200	.104	-.081	.514
9. Still in Tx Week 4	o											-	-	.421	<.001***
	d											-	-	.421	<.001***
10. Still in Tx Week 12	o													-	-
	s													-	-

Note: o= original data, s= data without SSRT outliers *p < .05, **p < .01

Table 2

Mean, Standard deviation and Effect sizes for participants still in treatment at week 4 and 12.

Measure		Retained			Dropped out			*t (p)*	BF01	*d*
		M	SD	N	M	SD	N			
Top-down inhibition (SSRT, ms)	Week 4	500	119	53	547	122	12	1.23(.224)	.563	.393
	Week 12	494	104	29	520	132	36	.84(.405)	.344	.209

Table 3

Hierarchical linear regression of associations between dependence and cognition

	Top-Down (SSRTms)		
Variable	*t*	*p*	R^2
Model 1			.04
Dependence	-1.62	.111	
Model 2			.07
Dependence	-1.79	.08	
WTAR	1.47	.15	
Model 3			.15
Dependence	-0.19	0.85	
WTAR	1.60	0.11	
Depression	-0.30	0.77	
Anxiety	-2.01	0.05	

Note: * Significant result, $p < .01$.

Table 4

Hierarchical logistic regression of associations between cognition and treatment outcomes

Variable	Week 4				Week 12			
	Odds ratio	95% CI	*p*	R^2	Odds ratio	95% CI	P	R^2
Model 1				.038				.004
Top-down (SSRT ms)	1.00	(0.99-1.00)	.252		0.99	(0.99-1.00)	.652	
Model 2				092				.012
Top-down (SSRT ms)	1.00	(0.99-1.01)	.165		0.99	(0.99-1.00)	.733	
Bottom-up (Compulsivity)	1.11	(0.96-1.28)	.154		1.03	(0.93-1.15)	.571	
Model 3				.133				.013
Top-down (SSRT ms)	1.00	(0.99-1.01)	.266		0.99	(0.99-1.00)	.703	
Bottom-up (Compulsivity)	1.12	(0.97-1.29)	.120		1.03	(0.92-1.15)	.563	
WTAR	1.04	(0.97-1.12)	.228		1.00	(0.96-1.05)	.823	
Model 4				.159				.051
Top-down (SSRT ms)	1.00	(0.99-1.01	.184		0.99	(0.99-1.00)	.571	
Bottom-up (Compulsivity)	1.11	(.95-1.18)	.180		1.04	(0.93-1.17)	.447	
WTAR	1.04	0.97-1.11)	.284		1.01	(0.9.6-1.06)	.708	
Anxiety	1.13	(0.89-1.45)	.306		1.05	(-.75-1.07)	.226	
Depression	0.97	(0.86-1.09)	.612		1.05	(0.96-1.15)	.303	
Model 5				.387				.087
Top-down (SSRT ms)	1.01	(1.00-1.02)	046		0.99	(0.99-1.00)	.459	
Bottom-up (Compulsivity)	1.00	(0.84-1.20)	.972		1.07	(0.94-1.21)	.286	
WTAR	1.03	(0.96-1.11	.403		1.01	(0.96-1.06)	.630	
Anxiety	1.17	(0.89-1.53)	.261		0.91	(9.75-1.09	.307	
Depression	0.98	(0.84-1.15	.819		1.06	(0.95-1.17)	.314	
Readiness to change	1.06	(0.97-1.14)	.178		0.98	(0.95-1.03)	.510	
Baseline cannabis use	2.02	(-0.87-4.70)	.102		0.94	(0.84-1.06)	.326	
Dependence	1.00	(0.97-1.04)	.777		0.99	(0.98-1.02)	.835	

Note: * Significant result, $p = .05$.